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A Journal of Neurology

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THE NEWER KNOWLEDGE OF VIRUS DISEASES OF THE NERVOUS SYSTEM: A REVIEW AND AN INTERPRETATION.

BY E. WESTON HURST.

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RECENT years have seen a considerable extension of our knowledge in the field of neurotropic viruses. The advance might have been greater but for the fact that much of the work done has been one-sided, usually by workers with little special knowledge of the nervous system [24], less often by neuro-histologists who have dealt with the end results of virus activity in the nervous system and have neglected entirely the experimental investigations which alone could answer many of the questions they have asked concerning pathogenesis. A review taking into account both the viruses and the terrain on which they manifest their activity will be of service in showing not only what has been accomplished in this sphere, but also the numerous gaps to be filled before we can begin to do more than guess at the fundamental processes involved.

DEFINITIONS.

At the outset it is essential that an exact meaning should be attached to certain terms qualifying the viruses under discussion. There is to-day much evidence to support, and but little to contradict, the belief that viruses are obligatory intracellular parasites [23]; also it cannot be doubted that among themselves viruses differ greatly in their cellular affinities. We may, therefore, reasonably hope that more complete knowledge will lead to a classification, based on the precise cellular tropisms of its members, of a group of contagia at present recognized only by the expression of their pathogenic tendencies.

Any but the most superficial analysis shows that many of the

peculiarities of behaviour which might be taken as criteria of neurotropism in a particular virus are not exhibited by all viruses which may fairly be designated neurotropic. This difficulty in establishing criteria does not, however, justify the indiscriminate use of the adjective, with which, apparently, many writers qualify any virus capable of evoking an intradural lesion, whether that lesion affects primarily the nervous elements or not. Such confusion of thought is implicit in the nomenclature even of so distinguished a contributor as Levaditi. For example, this author uses the term " ectodermoses neurotropes " [16, 17, &c.] to cover a group of diseases including rabies, poliomyelitis, herpes and vaccinia. Apart from some recent unconfirmed observations [171], it has never been shown that the first two viruses have any affinity for the surface ectoderm ; the herpes virus attacks and produces specific lesions in cells derived from all three embryonic layers ; while, as Levaditi himself showed, cerebral vaccinia is primarily a process in the mesoderm of the nervous system, and elsewhere in the body this virus evokes mesodermal lesions. Levaditi's more recent " mesodermose neurotrope " [98] in relation to the virus of lymphogranuloma inguinale has even less precise significance ; on the one hand the virus is not neurotropic in the commonly accepted sense of invading the central nervous system from a focus of peripheral inoculation, on the other it manifests no special affinity for the mesoderm of the brain as opposed to the mesoderm of the body generally. It is but one step further to class the tubercle bacillus as a neurotropic organism because on occasion it is the cause of tuberculous meningitis. The present writer can find only one characteristic common to all viruses which can legitimately be termed neurotropic—namely, that they all attack, primarily and directly, the nerve cell.

In this paper, then, " neurotropic virus " will be held to signify a virus capable of primary and direct attack on the specific nervous elements—nerve cells, and, in many cases, glial cells. Some such viruses have no apparent affinity for other cells and tissues ; these are the "stricter neurotropes." Many viruses, however, while demonstrably neurotropic also possess obvious affinities for non-nervous tissues ; these will be designated " pantropic " [139]. Finally, in the case of viruses exhibiting no apparent tendency to invade the central nervous system from a focus of peripheral infection, and which, when inoculated directly into the brain, create lesions by virtue of a primary action on the mesoderm, the perhaps less satisfactory term " viscerotropic " will be employed. When using these terms it is necessary in some cases to state clearly the

animal species on which observations have been carried out, since a virus may behave quite differently in different hosts. Thus the virus of herpes febrilis produces in man a superficial vesicular lesion, while in the rabbit many strains invade the nervous system to set up encephalitis [61]. The pseudorabies virus again is pantropic in the rabbit [139], but apparently strictly neurotropic in the rhesus monkey [140].

Histological Features of Virus Diseases.

Lesions in the Nervous System due to Neurotropic Viruses.

In all probability viruses are obligatory intracellular parasites [23]. If, therefore, the adjective neurotropic as applied to certain viruses has any significance, we should logically expect such viruses to be capable of a primary and direct attack on the nerve cells. Such is in fact the case. Yet the older literature on so typical a neurotropic virus disease as poliomyelitis ascribed the lesions in nerve cells wholly or in large part to impaired nutrition, resulting from interstitial inflammation, &c.; almost alone among the older authors Rissler [130] recognized the true sequence of events, recently emphasized by many [101, 103, 104, 113, 114, 121, 122, 128, 133].

The truth of this matter cannot be ascertained by studying human post-mortem material in which tissue and vascular reaction have had time to appear and dominate the histological picture: only examination in the earliest phases of the disease, as is possible in the experimental animal, can determine the structures first affected and the relative importance of the various changes seen later. A further point needing mention is that of technique. The German influence in neuropathology has rightly made the Nissl method the standard staining process for the nervous system. But in the study of lesions caused by viruses the technique suffers from serious defects. It is incapable of revealing clearly the cytological alterations most characteristic of such infections, and the preliminary fixation required by the method is not well adapted to their demonstration. Again, in the last stages of nervous degeneration the necrotic neurons are displayed far more effectively by other means. In fact, the use of some such fixative as Zenker with acetic acid, or sublimate-formol, and staining with phloxin- or eosin-methylene blue, Giemsa or even hæmatoxylin and eosin, are far more useful for proper evaluation of the histological picture of virus diseases of the nervous system than is the Nissl method.

The microscopical appearances of nerve cells affected by a virus vary with the acuteness or otherwise of the disease process. In hyperacute and acute conditions, and hence commonly in experimental infections

with viruses of exalted virulence, though also not infrequently in some naturally occurring infections, the type lesion is acute necrosis of the neurons. The cytoplasm is shrunken and strongly eosinophilic, the nucleus pyknotic, karyorrhectic, fading or absent; in the brief pre-necrotic phase various types of neuronal change described by Nissl may be seen, but especially the so-called ischæmic cell-change and the "severe cell-change." The more virulent strains of poliomyelitis virus acting on the monkey's cord destroy many of the cells of the anterior horns in this abrupt manner, and if the animal is sacrificed at just the right moment the histological picture may be almost uncomplicated by the rapidly following cellular exudation [114]. Similar necrosis may be met in one situation or another in experimental rabies [148, 163, 169], louping-ill [79, 80, 85], herpetic encephalitis [59, 69], equine encephalomyelitis [55], yellow fever [217, 218], pseudorabies [138], virus III infection [212], &c., either from catastrophic destruction within but a few hours, or from rather less acute degeneration often accompanied in the earlier stages by the formation of specific inclusions. In extremely acute infections, e.g. pseudorabies in the rabbit [138], the animal may die before further developments have time to occur, and the picture is then unequivocally that of primary and direct attack on the nerve cells. Usually, however, the animal survives longer, and then, as in all lesions accompanied by necrosis of tissue, polymorphonuclear leucocytes migrate swiftly into the damaged areas to attack and lyse the dead cells. These leucocytes, which may even penetrate the vacuoles of an incompletely necrotic neuron, themselves soon manifest karyorrhexis and other degenerative phenomena, and if death is still further delayed they are engulfed together with persisting remnants of the ganglion cells by microglial phagocytes; oxydase granules may persist in the nervous tissues longer than do recognizable leucocytes [114]. Many descriptions of these later changes have been contributed to the literature by writers who have failed to detect or correctly evaluate the essential primary pathological process in the neurons.

Side by side with this extremely acute destruction, slower forms of degeneration of nerve cells may obtain; in many diseases, e.g. poliomyelitis and rabies in man, they are the principal or only feature. It is in neurons so affected that, in the diseases in which they occur, cellular inclusions are most fruitfully sought. These inclusions may be sufficiently distinctive to be of diagnostic value, but their present interest lies in the support they afford to the theory of intracellular parasitism of the virus. Nerve cells succumbing to the slower forms of degenera-

tion are phagocyted by the microglia without leucocytic intervention, though cells of the lymphocytic series may make their appearance in the tissues. Diffuse and focal microglial proliferation thus comes to be a prominent finding in many virus diseases; the Babes nodules [149], supposed to be characteristic of rabies, and Wickman's polyblasts in poliomyelitis [135] are of this origin. Generally speaking, tissue infiltration is more marked in the less acute conditions—in this respect human may be contrasted with monkey poliomyelitis. In slowly progressive maladies (e.g. Borna disease) it is more difficult to demonstrate the primary attack on the nerve cells except in so far as these exhibit specific cytological alterations, presumably because the sensitive mesoderm reacts to the earliest changes in the nerve cells while there is still little alteration of the normal microscopical picture.

Finally, in every virus disease a proportion, often considerable, of ganglion cells remains apparently unaffected. It is rather exceptional to find inclusions in otherwise normal cells, though this does occur in the cornu Ammonis in rabies [186], and in Borna disease [41]. Nicolau, Nicolau and Galloway's contention that the presence of the inclusion represents the successful termination of the struggle between virus and cell is certainly not of general application, for in pseudorabies [138], infection with B. virus [37], yellow fever [221], &c., the earliest change in still normal cells which will later undergo necrosis is the development of acidophilic nuclear inclusions; and this process is not to be sharply separated, as Nicolau, Kopciowska and Mathis maintain [221], from the ultimate necrosis of the cell.

In some infections (e.g. pseudorabies, herpes, and infections with B. virus and virus III) the true glia demonstrably shares in the degeneration, and shows inclusions similar to those in the nerve cells; in other diseases, e.g. poliomyelitis and rabies, changes in the glia may well be wholly secondary and reactive. Where over considerable areas the glia accompanies the neurons to complete destruction, subsequent softening and porencephaly may result [18, 60, 140]; with less severe damage a glial-mesodermal scar is the outcome [74, 140], while still less profound injury leads to a pure glial sclerosis [117, 134, 135]. In subacute conditions, such as Borna disease, quite definite activity on the part of the glia may be evident at death.

While, therefore, degeneration in nerve cells and perhaps in glial cells is clearly primary, and at an early stage and in some localities of the nervous system may occur in the absence of any trace of inflammation in the mesodermal structures, this latter phenomenon is an integral part

of the later histological picture of most diseases due to neurotropic viruses. Perivascular cuffing often tends to be more marked around the third and fourth ventricles and the iter of Sylvius than elsewhere, even though maximal involvement of nerve cells is encountered in other regions. There is, however, considerable individual variation in the site of maximal reaction, as, for instance, the literature on rabies [152, 166, 168, 172, 175, 176, 181, 182, 184, 185, 187, 190] exemplifies. Like tissue infiltration, perivascular and meningeal exudations are more intense in subacute than in acute infections, but it is seldom doubtful how far they represent a secondary reaction to damage to the ectodermal tissues, and how far a direct and coincident action of the virus on the mesoderm. Thus, observation at successive stages of the various infections renders it certain that in many instances meningeal infiltration represents merely an overflow of inflammatory cells from the overcharged perivascular spaces of the nervous substance [105, 114], though belief in a primary meningitis in poliomyelitis delayed for many years a true conception of the disease. On the other hand, in some diseases meningitis is certainly due to direct action of the virus; thus in pseudorabies in the rabbit [138], B. virus disease [37] and virus III infection [212] the presence of nuclear inclusions in, or even acute necrosis of, meningeal and vascular elements proclaims the specific nature of the lesion. In the latter event polymorphonuclear leucocytes abound in the cellular exudate, though ordinarily, even with many leucocytes in the tissues, mononuclears predominate, and in subacute conditions are the only cells present. After the first few days the mesodermal reaction is the striking histological feature, and it may still be conspicuous months after the initial injury [60, 134, 140].

Perivascular hæmorrhages are frequently described as part of the histological picture of acute poliomyelitis, &c., and there can be no doubt that they are sometimes present. But caution is necessary in interpreting this finding. Small hæmorrhages are readily produced by rough handling during removal of a normal nervous system, and with greatly congested vessels in an acutely inflamed organ it is probably impossible to guarantee their absence. Boemke [5] has recently adopted this attitude in relation to the lesions described as characteristic of electrical shock. It is surely significant that scarcely ever, if indeed ever, are signs of reaction to the effused blood detectable [114]; in view of the work of Carmichael [6] and others such hæmorrhages can have preceded death by at most only a short time.

So far there is no sure evidence that any of the primarily demyelinating diseases are due directly to the action of a filtrable virus.

Lesions in other Viscera due to the Foregoing Viruses.

According to their action on organs other than the nervous system, the neurotropic viruses fall into three groups. Except when they are of the nature of a general response to infection, the lesions evoked in the general viscera by members of the first group (stricter neurotropic viruses, such as the viruses of rabies, Borna disease, &c.) occur primarily in connection with the nervous apparatus of the organ. Thus the infectivity of the buccal secretions in rabies has been associated with the presence of Negri bodies in nerve cells immediately underlying the mucosa, coupled with minute abrasions of the epithelium [173]. In Borna disease characteristic nuclear inclusions are found in the visceral nerve cells in many situations [22]. As examples of the second group the pseudorabies, B., and herpes viruses and virus III may be cited. These are pantropic, and, in addition to producing lesions in nervous tissue, they can under suitable conditions excite specific lesions, usually focal necroses, in many tissues and organs by direct parasitism of their constituent cells and independently of their nervous mechanism [37, 38, 64, 66, 75, 138, 139, 211, 213]. It is with viruses of this second group that specific lesions, such as inclusions and necrosis, are often found in the mesodermal tissues of the pia-arachnoid, &c. With a third group, including equine encephalomyelitis, neurotropic yellow fever and louping-ill viruses, the lesions in the nervous system are very like those caused by members of the first group, and encephalitis is the dominant clinical feature of the infection; these viruses do, however, grow in and exercise their pathogenic action on extraneural tissues, particularly on vascular and epithelial structures, and in this sense are pantropic [56]. As will be seen later, experimental study throws more light on their peculiarities than does histological investigation.

Other Viruses Capable of Evoking Intracranial Lesions.

The foregoing sketch outlines in very general terms the sequence of events in the nervous system infected with the more fully studied neurotropic viruses. Except for virus III, the organisms mentioned are those which under natural circumstances or after inoculation into non-nervous tissue may excite encephalomyelitis; experimental investigation usually reveals their ability to invade and parasitize the central nervous system from a focus of peripheral inoculation. The present-day tendency to inject each and every virus intracerebrally has brought to light the capacity of several, which under natural conditions are the

causative agents of diseases in which encephalitis constitutes no part of the clinical or pathological picture, for evoking severe and often fatal inflammation when introduced directly into the brain. The resultant lesions differ fundamentally, however, from those described above, and in the writer's opinion it is not justifiable to classify the organisms responsible, as do some workers, with the neurotropic viruses.

Vaccinia is an example of this kind. During or after the systemic reaction to vaccination, especially with "generalizing" strains, virus may sometimes be detected in the cerebrospinal fluid [202] or nervous tissue [204, 206]; it may persist here in the absence of lesions for as long as forty-one days [201]. Its localization in the brain is facilitated by trauma [204]. Injected extracranially, even into a nerve [201], the virus probably never causes a primary encephalitis, though sometimes the lesion mentioned below may accompany very severe generalized vaccinia [204 and personal observation]. Neurovaccine does not differ materially from testicular or dermal vaccine in its affinity for the brain [209]. Following direct intracerebral or intracisternal inoculation the pathological changes are primarily meningeal, and alterations in the underlying cortex are similar to those accompanying any severe meningitis [203, 205, 207, 208].

The descriptions of the lesions evoked by intracerebral inoculation of the salivary gland virus of guinea-pigs leave little doubt that here again there is a primarily mesodermal reaction (194-195·5). Andrewes [193], it is true, found minor lesions in the nerve cells of the lumbar cord, while in a single guinea-pig he observed intranuclear inclusions in a few nerve cells of the brain; later in his paper, however, he suggests that in this disease the inclusions in the meninges, and presumably those in the brain, may in all probability be regarded as denoting not multiplication of virus, but merely reaction to its presence, and hence have a significance different from that of the inclusions produced by virus III.

Thirdly, most writers agree that after direct intracerebral injection of the virus of lymphogranuloma inguinale an almost pure mesodermal lesion develops [94-96, 98]; the demyelinating condition described by Jonesco-Mihaiesti *et al.* [97] probably resulted from spontaneous disease in the experimental animals [93, 99]. Inoculated by other routes the virus appears to have no affinity for the undamaged [95] or even the damaged [98] nervous system.

In brief, none of these viruses shows particular affinity for nervous tissue; after intracerebral inoculation they merely excite lesions in the mesodermal structures covering and penetrating the brain, as they do

under other circumstances in mesodermal and other tissues elsewhere in the body. To classify them as neurotropic is to rob the adjective of any precise meaning, and they are here referred to as viscerotropic viruses.

The Nervous Lesions Due to Some Viruses Less Fully Studied.

In the case of certain other viruses affecting the nervous system our knowledge is still too incomplete to permit of categorical statement, which must be based on adequate experimental as well as histological study.

In dog distemper the nervous system is frequently if not invariably involved together with the general viscera. Not only do the older accounts of the histological findings stress the later reactive phenomena, but in the past infections not due to the virus have been mistaken for distemper. Dunkin and Laidlaw's account of the lesions in the ferret and dog [46] suggest a direct attack by the virus on the nerve cells, as do some of Cerletti's findings [45]. Inclusion bodies of several types have been described in the neurons [44, 47, 48, 50, 169, 192]. The relation of the demyelinating lesion of Perdrau and Pugh [49], or the mixed lesion of Marinesco *et al.* [48] to distemper awaits elucidation.

In the rather similar, though ætiologically distinct, epizootic fox encephalitis [51-53], an apparently direct attack on the ectodermal tissues of the nervous system is overshadowed by vascular lesions in the brain and elsewhere. The presence under certain circumstances of intranuclear inclusions in ependymal cells betokens a degree of ectodermal parasitism of the virus, though the chief feature of the disease is the widespread affliction of vascular endothelium and cells of the reticulo-endothelial system. In a personal communication Dr. R. G. Green informs me that the demyelinating lesion described by Levaditi *et al.* [54], is certainly not typical of the disease, occurring in his experience in only a single animal; it may possibly bear a similar relation to fox encephalitis as does the Perdrau and Pugh lesion to dog distemper, or alternatively may represent another disease entity.

The virus responsible for the St. Louis outbreak of encephalitis [196-200] apparently behaves as a typical neurotropic virus causing necrosis of the nerve cells and other lesions already considered. On the other hand, the virus of lymphocytic choriomeningitis [88-92] appears unusual in that it is the first known virus commonly giving rise under conditions of natural infection to a purely mesodermal lesion in the nervous system.

In the absence of precise knowledge of its experimental behaviour, the exact position of the hog-cholera virus also is hard to define. The nervous lesions of this malady [77, 78] differ from those typical of neurotropic virus diseases in being more or less evenly scattered over grey and white matter, and in a very considerable vascular involvement equally or more marked in organs other than the brain. It is tempting to regard this process as a systemic one affecting the nervous system largely by virtue of its nutritive apparatus.

Conclusions.

On histological grounds we may therefore consider the better-known viruses attacking the nervous system as belonging to two classes, according to whether they strike primarily at the specific neural elements, or exercise their pathogenic action mainly on the mesoderm. The former can be subdivided by their capacity or incapacity for parasitizing non-nervous elements within the nervous axis or elsewhere. If these distinctions are significant, we might anticipate that they would lead to differences in the mode of spread of members of the respective groups, and it is here that the available experimental evidence, fragmentary though it may seem a few years hence, is of value.

Experimental Data on the Routes of Infection of the Nervous System.

Spread by the Nerves.

Peripheral nerves of any size consist of medullated and non-medullated nerve-fibres bound together by fibrous tissue. The larger trunks are nourished by special vascular branches, and contain lymphatic channels concerning the central relations of which our knowledge is singularly unprecise. The trend of modern opinion is to believe that centrally these perineural lymphatics do not connect with the subarachnoid space [*see* Abel *et al.*, 1, 2]; such observations as those of Horster and Whitman [12], in which material inoculated intraneurally arrived at once at the nervous axis, in all probability merely indicate that sufficient pressure during injection can rupture the existing barriers, demonstrated histologically by Elman [10]. Some indirect evidence supporting this view will be mentioned presently. The medullary sheaths are interrupted at the nodes of Ranvier, and it seems inconceivable that the relatively inert myelin can provide a medium for rapid transport to the central nervous system; the neurolemmal sheath is highly tenuous except in the vicinity of the nuclei of the cells of Schwann. The axis cylinder, a direct protoplasmic continuation of the body of the neuron, seems to be the chief uninterrupted link between centre and periphery. De Renyi's micro-dissection studies [9] indicate apparently that it, like the rest of the cytoplasm of the nerve cell, is of a very definite consistency, retaining its shape completely when cut into fragments. It is intimately connected with the medullary sheath, leaving no natural peri-axial space; the myelin and neurolemma are less closely joined.

Thiele and Embleton [29] believed that the more soluble substances at least may pass directly up the axis cylinders to the cord. Yuien [35], on the other hand, found that solutions injected into a nerve were conveyed by the perineural spaces to the junction of the anterior and posterior roots, thence by the anterior root to the pia and subpial spaces of the cord, and also along,

though not apparently within, the motor root fibres as far as their cells of origin. If sufficient time were allowed the solution passed outwards along the posterior roots, but not along the contralateral anterior root. This and other experiments showed that in the motor nerve the direction of lymph flow is centripetal, in the sensory nerve centrifugal. It should be remarked that in the animal killed one and a half hours after inoculation the solution had already reached the cord, an observation recalling the experience of Horster and Whitman (*loc. cit.*); there is no evidence that viruses travel at this speed.

Sullivan and Mortensen [28·5] injected 0·05 c.c. brominol coloured with scharlach R into the sciatic nerves of rabbits and cats, and by radiography traced its subsequent passage towards the cord; they claimed that after four to six hours gross dissection revealed the coloured oil in the subarachnoid space. The rate of spread was not appreciably diminished when muscular movement was prevented by administering hypnotics.

Using the same solutions as Yuien, Hurst (unpublished experiments), injected the median nerves of monkeys at the level of the bend of the elbow. One, two and a half, four and a half, and seven hours later, no macroscopic or microscopic deposit of Prussian blue could be detected above the cords of the brachial plexus. As time elapsed the reaction at the site of inoculation became progressively weaker, until after twenty-four hours no Prussian blue was precipitated even here. Microscopically, at the level of injection the blue precipitate lay mainly under the connective-tissue sheaths of the nerve bundles and, to a less extent, around small vessels deeper in the bundles; the axis cylinders were coloured diffusely a pale blue for a short distance on either side of the nodes of Ranvier, which are recognized as regions of comparatively great permeability.

In a personal communication Dr. D. Denny-Brown states that though injection of a peripheral nerve of cat or monkey with indian ink or carmine-gelatine most often produces merely a local distension of the connective tissue, occasionally the injection will run some centimetres under the perineurium without pressure. When this occurs from an injection fairly near the cord the inoculum may run under the sheath of the spinal ganglia and pass into the subarachnoid space. The exact pathway of this communication is under investigation, but no evidence has been obtained to show any natural circulation by this route.

The anatomical relations of the olfactory nerve differ from those outlined above. The terminal fibrils are freely exposed on the surface of the olfactory mucosa. The lymphatic channels accompanying the nerve filaments, distinct from the general lymphatic system of the nasal mucosa, connect directly with the subarachnoid space [3, 7, 34], and it has been shown that they furnish ready access to the meninges in the case of bacterial invasion [30, 31].

Experimental evidence of the importance of the nervous pathway in the transmission of rabies [151, 153, 154, 161, 183-185] dates back for many years. Rabies did not develop after intrasciatic inoculation if at

the same time the nerve were sectioned and cauterized on the central side; if an inoculated tail were removed within twelve hours of the deposition of virus no disease resulted; section of the nerve supply of a salivary gland prevented infection of the secretion; virus and lesions appeared first in that part of the cord most nearly connected with the site of inoculation. In the case of poliomyelitis similar evidence was available [125, 131, 136]. Centripetal neural spread has since been demonstrated in other virus diseases [36, 63, 67, 69, 70, 72, 139], while Nicolau, Nicolau and Galloway have emphasized the centrifugal march of viruses injected intracerebrally; a remarkable example of the latter phenomenon is furnished by Borna disease, in which the long incubation presumably enables the virus to penetrate to, and produce specific changes in, the most remote ganglia of the peripheral nervous system [22, 43]. Evidence of such spread may, however, be obtained even in some hyperacute conditions [139]. In rabies the possibility of this occurring through the medium of the blood has been eliminated [178, 179]. To the transmission of viruses along pre-formed paths Marinesco has applied the term odogenesis.

Until recently less attention has been paid to the precise transmitting mechanism in the nerves; usually it has been assumed or implied that the perineural lymphatics convey the virus to the cerebrospinal fluid, which then acts as the agent of dissemination to various parts of the nervous system [26]. As has been pointed out, it is by no means certain that such a course is anatomically possible except in the case of the olfactory nerve. Moreover, in poliomyelitis it is exceptional under experimental conditions to recover virus from the fluid [109, 115], at any rate during the incubation period, and in the human disease no such finding is on record [100, 102, 112, 123, 127, 131] [1]; we have seen also that meningitis is not the primary lesion of the disease as was once supposed. In rabies negative results have usually been reported [157, 165, 180]; positive results have sometimes been obtained during the period of nervous symptoms [156, 162, 167]. Herpes virus is not easily found in the fluid in rabbits [63]; it has been detected in human fluid [62] in a case where it was certainly not responsible for the nervous condition present. In any case, recovery of a virus from the fluid when the disease process in the nervous tissue is at its height does not necessarily indicate the path travelled during the incubation period.

[1] In view of the difficulty of establishing human poliomyelitis virus in the monkey, too much weight should not be attached to the negative results with human cerebrospinal fluid and blood. For the monkey, and in the case of rabies virus, the above argument holds good.

Following previous unsuccessful attempts to detect virus in the fluid during the incubation period of experimental poliomyelitis, Hurst (unpublished experiments) practised intrasciatic inoculation in a monkey; each day during the pre-symptomatic period as much fluid as could be removed with safety (about 3 c.c.) was used to replace that of a fresh animal, which thus received in all perhaps 12 c.c. fluid. Nevertheless it did not develop the disease. Repetition of the experiment again led to a negative result. It is very difficult to believe that in these instances the fluid played any part in the transportation of the virus.

It must, of course, be admitted that experimental infection of the fluid readily produces disease. In experimental poliomyelitis it seems that intracisternal inoculation is followed by penetration of the ependymal surfaces by the virus, after which the course of events is similar to that following intracerebral inoculation [116]. In rabies Speransky found that inoculation into a walled-off area bounded only by meninges led to disease only after great delay; he concluded that the cerebrospinal fluid greatly assists in disseminating the virus [191]. No doubt it does when virus is introduced directly into the fluid, but neither of the observations cited show that this occurs under normal conditions.

On the other hand, there is a growing mass of evidence that the nerve fibres themselves may provide the path to the central nervous system. Although Duboué as far back as 1879 suggested the axis-cylinders as a pathway of infection in rabies [155], and in the case of other diseases the supposition has been again advanced by later writers, notably Levaditi, Goodpasture's observations [65, 67] were the first which can be regarded as affording reasonably clear evidence of this occurrence. After inoculation of herpes virus into an area supplied by the sensory division of the 5th cranial nerve, lesions appeared at a point immediately central to the plane where the sheath of Schwann disappears; in these fibres the myelin sheath is not sufficiently developed to prevent escape of virus into susceptible tissues. In the motor division of the nerve, however, conditions are different, inasmuch as the myelin sheaths are much more substantial; after inoculation into the masseter muscle, the first intracerebral lesions are in the motor ganglion cells of the 5th nerve nucleus, and the heavily medullated fibres pass through a wide zone of susceptible tissue without evidence of neuroglial infection. In the case of rabies less conclusive evidence of axonal spread was forthcoming [160]. However, Marinesco and

Draganesco [20] reported that inoculation of herpetic material below a strongly compressed segment of the sciatic nerve, in which the axons had been completely interrupted, might lead to the disease, and concluded that transmission must have taken place by the perineural lymphatics. Even if these channels do connect with the spinal theca the two views are not necessarily in conflict; in the nerve infection may travel by both routes, but more quickly and favourably by the axis-cylinders. Indications in pseudorabies that the virus causing interstitial lesions in the nerve is not responsible for those in the spinal ganglia, which appear before the ascending neuritis has mounted to the juxta-medullary part of the peripheral nerve [138], support this view; similar histological observations are on record in herpes [72] and in B. virus disease [37]. In B. virus disease the meninges are susceptible to direct attack of the virus, which after intracerebral inoculation evokes specific lesions here, but when myelitis ensues after peripheral inoculation specific changes are seen usually only inside the cord, and not in the meninges through which the infective agent must have passed; this observation again suggests an insulating structure between the susceptible meningeal tissues and the virus, which must in other words be inside the medullary sheaths of the nerve fibres. Returning to Marinesco and Draganesco's results, the fact that the herpes virus is not a strict neurotrope and may infect other tissues, as poliomyelitis and rabies apparently cannot do, may conceivably have an important bearing in allowing it to go through a natural barrier between the perineural lymphatics and the subarachnoid space. A further possibility, that the results were due to the mechanism operative in pseudorabies after inoculation into a denervated area, will be considered later.

In a number of diseases caused by neurotropic viruses it has been remarked that a certain amount of trauma exposing the axis cylinders is necessary to ensure successful intraneural inoculation [71, 115, 159].

In poliomyelitis, Fairbrother and Hurst's study of the march of virus and of lesions during the incubation period, suggested very strongly that this virus also may spread by the axons [109, 115]. Without entering into details, one series of observations may be mentioned which is difficult to explain on any other supposition. After inoculation into the left sciatic nerve the virus first appeared in the lumbar cord, and soon afterwards in the leg area of the right motor cortex. At this time the cervical cord, the arm area of the right motor cortex and the left motor cortex were free from virus. Later, virus appeared in the cervical cord, the leg area of the left motor cortex and in the arm area of the

motor cortex of both sides. This behaviour would be expected were the pyramidal fibres the transmitting structures. Similar conclusions have been reached by Faber and Gebhardt in a very detailed study of the disease following nasal instillation [108]. Brodie and Elvidge [106] record that partial bilateral removal of the olfactory bulbs and tracts prevented infection from nasal instillation, and Schultz and Gebhardt [132] a similar finding after cauterization of these structures; in view of what follows, however, in respect to the recently studied virus of equine encephalomyelitis (*q.v.*), these observations can no longer be accepted as indicative of axonal spread unless it be shown that the operative procedure had not led also to cicatrization of the accompanying perineural lymphatics. Jungeblut and Spring [119] observed that after section of the spinal cord in the dorsal region, followed by intracerebral inoculation, poliomyelitis virus did not pass into the lower segments of the cord despite the fact that the circulation of cerebrospinal fluid was unimpeded. The occurrence of crossed paralysis noted by some observers [109, 131] after intracerebral inoculation has been denied by others [105].

O'Leary and his co-workers [126] dissent from the interpretation placed upon some of the foregoing observations. Using the cathode ray oscillographic technique they found that the functional activity of the nerve fibres of poliomyelitic animals remained normal until the period when histological changes were clearly demonstrable in the nerve cells. They believe that if the virus travelled by the axis cylinders signs of impaired conductivity should be manifest at an earlier stage; as an alternative they suggest that possibly the virus travels between the nerve fibres, and would explain Hurst's results after sciatic inoculation on the ground that the path of least resistance lies between the pyramidal fibres rather than across them. It is probably impossible finally to prove or disprove this hypothesis, which in this case rests upon the assumption that the passage of virus along the axon is necessarily detrimental to that structure. This by no means follows from the evidence available. In several diseases due to neurotropic viruses it is possible to detect nuclear inclusions, indicating deranged nuclear metabolism, while the cytoplasm is still normal; in pseudorabies in particular, the Nissl substance, Golgi apparatus, mitochondria and neurofibrils may appear unaltered with quite advanced nuclear changes [138]. It may be that the presence of some viruses in the cytoplasm is relatively innocuous, and that it is by perversion of nuclear metabolism that impaired function of the cell and cytoplasmic degeneration are ultimately brought about. Were this so

the conductivity of the axon would remain unaltered during transmission of the virus. On the other hand, in equine encephalomyelitis in which no evidence of axonal spread of the virus is yet forthcoming [56], the distribution of lesions in the brain at an early stage following intranasal instillation is in large part determined by the course of the olfactory connections.

Cowdry [8] finds the physical factors involved in the suggested spread by the axons difficult to comprehend. "The processes are tubes of capillary size through which no chemical substance could travel without being arrested by practically complete adsorption on the walls." He also quotes the observations of de Renyi (*loc. cit.*) on the consistency of nerve fibres. The fact referred to above, that the nucleus of the neuron is often the first part of the cell to show damage, suggests that the virus must enter and act upon the nucleus itself; thus the problem of passage of virus through a semi-solid gel cannot wholly be avoided, even though minimized by the assumption that penetration of the cytoplasm does not occur until the cell body is reached. Except for this difficulty in explaining transmission, if viruses are obligatory intracellular parasites we might anticipate penetration of the neuron at the nearest point, i.e. in the case of peripheral inoculation at the nerve ending or exposed part of the axon, which after all is merely an extension of the cell body. In certain circumstances the alternative to axonal spread, viz. transport by the perineural lymphatics, is at least as difficult to envisage; in the case of a strictly neurotropic virus, such as that of rabies which does not multiply at the site of inoculation (personal observation), after introduction of a small amount by scarification we should have to postulate a regular fluid flow capable of delivering the virus without loss from the site of infection all the way from the nerve endings to the cord.

Levaditi imagines the propagation of viruses as taking place by infection of successive segments of the axon accompanied by the development of immunity and a refractory state in the parts previously affected (neuroprobasia, [69]). It seems, however, that this is pure hypothesis without adequate experimental basis. It has been shown [115] that in poliomyelitis excision of the sciatic nerve from the sciatic foramen downwards, within twenty-four hours of intraneural inoculation at the level of the popliteal fossa, prevents development of the disease, whereas the same procedure at thirty-six hours does not; Koppisch [68] has criticized this observation, partly on the ground that trauma may completely alter the rate of conduction of virus along the nerve, but his

own figures for the rate of transmission of herpes virus, 0·35 mm. per hour, are not vastly different. If they represent the speed of transmission of a virus, it is difficult to see how any immunity reaction, in the accepted sense of the term, could be evoked in so short a period of time. On the other hand, if, as seems doubtful, Yuien's experiments (*loc. cit.*) can be taken at their face value, this time is greatly in excess of that required for solutions to pass along the perineural lymphatics.

To conclude, the available evidence clearly establishes the importance of the neural path in infections of the central nervous system with the neurotropic viruses. It does not favour the belief that in the transport of virus the perineural lymphatics and cerebrospinal fluid take the major part; with Pette, Demme and Környey [129], however, we are far from denying that the fluid may at some stage play a subsidiary rôle. On the other hand a number of observations strongly suggest the possibility of transmission along the axis cylinders of the nerve trunks; the chief difficulty in the general acceptance of this belief lies in the physical constitution of the nerve fibre. It is obvious that much more work is needed to reconcile conflicting statements regarding the finer anatomy of the nerve trunks and the structure of the nerve fibre before universal agreement is obtained.

The Presence of Virus in the Blood-stream.

The nervous tissues are separated from the blood-stream by physiological barriers, the blood-brain and blood-cerebrospinal fluid barriers, which hold back many substances of even comparatively simple structure and low molecular weight. Most bacterial toxins and many dyes are thus prevented from reaching the nerve cells, though in this connection the electrical charge is possibly important [11]; antibodies also do not pass the barriers. It is not difficult to believe that circulating viruses, especially the larger ones, would likewise be denied direct access to the nervous structures, though it might equally readily be supposed that some might ultimately "grow through" the barrier by infecting the cellular elements concerned. The limited evidence available suggests that viruses do not easily penetrate the barrier. Thus McKinley and Holden [21] found that bacteriophage did not appear in the cerebrospinal fluid within twenty-four hours of intravenous inoculation. On the other hand, these authors claimed that the virus could pass in the opposite direction, from fluid to blood; in this case the effect on the permeability of the barrier of intrathecal inoculation of foreign material was not excluded as the essential factor, though Flexner and Amoss [110, 111] had previously demonstrated its operation in experimental poliomyelitis. Klieneberger [12·5] found only slight penetration of the barrier when enormous doses of bacteriophage were given intravenously. The virus of equine encephalomyelitis, of

comparatively small size, and the larger pseudo-rabies virus do not pass directly from blood to cerebrospinal fluid or nervous tissues [56, 139].

There is, of course, an abundant literature on the means whereby permeability of the barriers may be increased. In work with viruses slight trauma is often deliberately inflicted to circumvent the normal defence mechanism. Winkler [210] stated that vaccinial infection increases permeability to the bacteriophage. Le Fèvre de Arric and Millet [13-15] claimed to have favoured penetration by intraspinous inoculation of distilled water or hypertonic saline, and by intravenous injection of various chemicals and dyes; they worked, however, with viruses (herpes, rabies) which in untreated animals may under certain conditions produce nervous disease following intravenous inoculation. Demme [8·5] found that pathological conditions of the meninges and brain favoured the passage of bacteriophage from the blood.

In determining the rôle played by the blood in infections with the neurotropic viruses two considerations must be borne in mind. In the first place the same importance cannot be attached to the presence of virus in the circulating fluid at all stages of infection. Thus it would not be remarkable if on occasion in the later stages of a particular disease, coincidently with lysis and phagocytosis of destroyed nerve cells, positive blood tests were recorded. Of quite different significance would be the circulation, during the incubation period, of virus inoculated intranasally or intramuscularly, though, as will be seen presently, precocious infectivity of the blood is not necessarily a pointer indicating the route of invasion of the central nervous system.

The second consideration concerns the clearing mechanism of the blood. Viruses inoculated intravenously are, no doubt, dealt with in the same way as are visible bacteria. Within a few hours of inoculating a large dose of equine encephalomyelitis virus, none may be detected in the blood [56]. A large dose of pseudorabies virus so introduced disappears even more rapidly [139]; later, after the virus has undergone considerable multiplication in various viscera, the blood once more becomes infective. In some cases after subcutaneous inoculation of pseudorabies virus the lung and spleen may be infective when passage of the blood is negative, though, doubtless, this visceral virus has arrived by way of the circulation. These observations suggest that if a virus enters the circulation intermittently, even in considerable amounts, it is rapidly removed therefrom with restitution of sterility, and the blood infection remains inapparent; if passage of virus by way of the visceral nerves from the cord can be excluded, infectivity of the blood-rich organs may thus be a more delicate test for blood contamination than is afforded by single examination of the blood. The detection of virus in the blood

must mean either that it is entering the circulation continuously and in considerable amount, or that it is growing in the blood, as Gordon suggests in the case of louping-ill [83], or else that the normal clearing mechanism is no longer operative; failure to detect virus signifies the exact converse and nothing more.

The facts bearing upon the part played by the blood may now be presented, and in doing this it is again convenient to consider separately the different classes of viruses.

The stricter neurotropes.—To recover poliomyelitis virus from the blood is unusual, though small quantities may be present at the height of the disease [102, 107, 112, 123, 136]; in any case positive results at an earlier stage would probably have little significance in the pathogenesis of the nervous disease, since only with very large doses does intravenous inoculation lead to infection [107], and inoculation directly into the carotid artery is no more successful [118].

Rabies virus, too, is rarely found in the blood [150]; moreover, the criteria of infection in the passage animals of some of the earlier workers who claimed positive results would probably not now be accepted. Even if virus does occasionally appear in the blood, Schweinburg and Windholz' experiments [189] seem to show that the occurrence is without bearing on the invasion of the nervous system; into one animal of each of eighteen pairs of parabiotic guinea-pigs they inoculated rabies virus, and only the inoculated animals developed the disease.

Using reasonable amounts of virulent emulsion, most authors have found intravenous inoculation ineffective, though possibly different animal species vary somewhat in their response [150]. Schweinburg [188] states that to ensure positive results it is not always necessary, as Jowelew [164] maintains, to break down the hæmato-encephalic barrier by "pumping"; in the guinea-pig 90 per cent. success is attained with large quantities of thick emulsion freed by paper-filtration from coarse particles. But the dosage needed amounts to 6 c.c. per kilo body-weight! Hurst (work to be published) has recently found that intravenous inoculation of virulent guinea-pig brain in the rabbit is much more effective than is that of homologous brain, and that infection is secured with quite small doses; the reason for this is at present under investigation.

Borna virus is not found in the blood [42]; Seifried [25] regards as exceptional Ernst and Hahn's results [39], in which virus was not only detected therein, but also passed through the placenta to the fœtus. Single intravenous inoculations are stated not to produce the disease

[40, 42], though the writer has sometimes been successful with large doses.

Practically no work has been undertaken to elucidate the method of infection of the central nervous system in the case of successful intravenous inoculation of viruses of this type. The one important observation is that of Lennette and Hudson [124] who found that repeated intravenous injection of poliomyelitis virus was ineffective if the monkeys were previously subjected to extirpation of the olfactory bulbs and tracts. Since they also found that following injection virus might be present in the nasal washings, the path of infection seems obvious. As will be seen later, work along other lines led the writer to a similar conclusion in the case of the equine encephalomyelitis virus.

The pantropic viruses.—These may or may not be detected with ease in the blood-stream.

In this respect the virus of pseudorabies is not consistent in its behaviour. During and for some time prior to the period of nervous symptoms in rabbits infected with the Aujeszky strain, the blood is usually infective in high dilution [142, 144, 147], though this may not have been so when the virus was first isolated [137, 139, 141, 143]. On the other hand, the serologically identical Iowa strain [146] is inconstantly present in even large volumes of blood [139, 145], though possibly with repeated passage this difference between it and the classical strain is less marked. Be this as it may, the observation that after subcutaneous or intramuscular inoculation virus and lesions first appear in the nervous system at the level directly connected with the site of inoculation [139] demonstrates that the blood is not the medium of transport to the cord, which, as with viruses of the preceding group, is invaded by way of the peripheral nerves. After intravenous inoculation virus appears in the nervous tissues no sooner than after subcutaneous or intramuscular injection; the fact that, in contrast to the stricter neurotropes, this virus infects very readily by the intravenous route must be related to its pluricellular affinities permitting it to establish infective foci in certain viscera, from which follows extension by the neural route. For the same reason virus introduced into a denervated area proliferates locally, invades the blood-stream, infects the general viscera, and ultimately reaches the nervous system by the visceral nerves [139].

The virus of herpes may sometimes be detected in the blood [69, 73], but, as already detailed, infection of the brain takes place through neural agency. Intravenous inoculation often leads to foci of necrosis in the adrenals and liver [67, 75, 76], which presumably form the starting point

for the not infrequent invasion of the nervous system [61, 67, 73, &c]. Local growth of virus followed by a non-apparent infection of the blood-stream, as suggested in the introduction to this section, might account for Marinesco and Draganesco's observation that crushing a peripheral nerve so as to interrupt completely the axons between the site of intraneural inoculation and the cord did not prevent the nervous infection [20] ; these authors accept this finding as evidence of spread of the virus by the perineural spaces. Usually, inoculation into a denervated area does not lead to nervous involvement [67, 69].

The B. virus has not yet been detected in the blood [36], but the presence of numerous necrotic foci in the viscera at an early stage after intratesticular inoculation [37], and less frequently with other routes of infection, are certain proof of blood contamination, apparent or inapparent. Just as with pseudorabies virus, intravenous inoculation of even small doses leads to the nervous disease. The histological and clinical findings certainly indicate neural spread to the nervous system.

The state of affairs with some other pantropic viruses (equine encephalomyelitis, yellow fever,[1] and louping-ill viruses) is quite different. At death following inoculation by a peripheral route, virus and lesions are usually localized to the nervous system, leaving the blood virus-free. But before the period of nervous manifestations these viruses may undergo considerable multiplication outside the nervous system, and the blood is often highly infective. It may be noted that in Nature these diseases are transmitted by the bites of blood-sucking insects [57-58·5, 86].

From the point of view of the mechanism of infection of the central nervous system, the virus of equine encephalomyelitis has perhaps been studied most completely. Introduced in even small doses intravenously or by some other route of peripheral inoculation [56], this virus appears sooner or later in the blood where its titre rapidly rises. After a time in the monkey virus disappears from the blood, and humoral immunity, as judged by the presence of neutralizing antibodies in the serum, is established ; the animal may thereafter remain well. But in about half the cases, when the monkey provides as potent an antiserum as it ever will, it develops encephalitis and dies. In the case of the guinea-pig a

[1] The differences between the ordinary " viscerotropic " yellow fever virus and the modified " neurotropic " strain are not as great as was formerly supposed. Theiler and Hughes [224] have shown that African monkeys said to be insusceptible to the viscerotropic virus may develop encephalitis on intracerebral inoculation, as do Asiatic monkeys in which the attack on the liver is frustrated by administration of antiserum. Similar observations are recorded by Findlay and Stern [217·5]. One variant may readily be converted into the other [216]. Thus the term " viscerotropic " has here a meaning different from that given in this review.

much higher percentage of animals contracts the nervous disease and dies, and the nervous phase follows much more quickly on the visceral, occurring perhaps before the blood is wholly virus-free. There is no evidence that infection of the nervous system takes place by way of the peripheral nerves in general; after inoculation intramuscularly, intradermally or intraneurally in the hind limb, virus and lesions do not appear first in the lumbar cord or intervertebral ganglia. In the monkey the cerebrospinal fluid is infective before many parts of the brain tissue, but after intravenous inoculation of large doses of virus several days elapse before the fluid becomes virulent, ruling out the possibility of direct passage through the blood-cerebrospinal fluid barrier. In the guinea-pig the frontal region of the brain is almost always virulent before the brain-stem and cord, as it is, though at an earlier stage of infection, after intranasal instillation of virus. During the period of blood-circulation of virus following intramuscular inoculation, virus may appear in the nasal washings: while in a certain number of cases, but not in all, after intramuscular inoculation the distribution of lesions is similar to that obtaining after intranasal instillation. In short, after inoculation by the intramuscular and similar routes the evidence points to a spread of virus from the blood to the nasal mucosa and thence to the brain as the most frequent occurrence.

Now since there is no evidence in favour of neural spread after intramuscular or intrasciatic inoculation, it does not seem likely that virus is transported from the nose by the fibrils of the olfactory nerve; the work already cited [3, 7, 30, 31, 34] suggests an alternative and more probable path by the perineural lymphatics accompanying the nerve. If this latter is the route utilized, there is no apparent reason why virus introduced into the sciatic nerve should not travel to the cord by the perineural lymphatics, unless these structures in the case of the peripheral nerves do not connect centrally with the subarachnoid space; the above observations, therefore, offer some support to the anatomical evidence that no direct connection exists. This conclusion in turn implies that such viruses as do pass along the peripheral nerves to the nervous axis, as poliomyelitis, rabies, &c., attain their objective by the medium of the axis cylinders.

It might be thought possible by experimenting with animals previously subjected to ablation of the olfactory bulbs to prove definitely that virus travels from blood to brain by way of the nose, especially as it seems likely that cicatrization following the operative procedure would block also the lymphatic connections. Unfortunately, the impaired efficiency

of the hemato-encephalic barrier following trauma to the nervous tissue persists for a very long time. It follows that with viruses circulating in the blood only negative results such as those obtained by Lennette and Hudson with poliomyelitis would be of significance. In the case of equine encephalomyelitis, infection of the nervous system still followed intramuscular inoculation in animals subjected two months previously to the operation indicated, though other observations suggested that the direct route from nose to brain had been blocked [56].

Occasionally after intramuscular inoculation of the virus of equine encephalomyelitis, the brain-stem and not the frontal region first becomes infective. Also, since the distribution of lesions following intramuscular inoculation is not always identical with that after intranasal instillation, we cannot assert that the path suggested above is the only one possible. On theoretical grounds it can be imagined that the virus may "grow through" the blood-brain barrier. During the phase of visceral infection the cells constituting the barrier may be infected, and virus may persist in them, as it does in the spleen, for some time after antibodies have appeared in the blood. Once immunity is established, virus escaping on the blood side of the barrier would be impotent in the presence of antibodies and resistant tissues, whereas virus leaking on the other side would find itself in a susceptible tissue shut off from humoral influences by the barrier; a fatal encephalitis might then ensue in spite of the visceral immunity. That this course of events is possible is shown by the observation that while a monkey which has passed the visceral phase of infection without having developed encephalitis will tolerate millions of infective doses of virus inoculated intramuscularly, it usually contracts encephalitis and dies if virus be inoculated directly into the brain [56].

Many of the facts established concerning the viruses of louping-ill [81-84, 87] and yellow fever [214, 215, 219, 220, 224] would fit in with the assumption that their mode of action is essentially similar to the foregoing, though it must be mentioned that Theiler [222, 223] has obtained apparently definite evidence of neural spread of yellow fever virus. There are, however, considerable gaps in our knowledge concerning these other viruses; a full discussion has been published elsewhere [56].

To conclude, detection of a neurotropic virus in the blood is likely only when the virus is entering the circulation more or less continuously and in large amounts, i.e. when large reservoirs of virus exist in the

tissues, or if it is actually growing in the blood. It is, therefore, unusual to find the stricter neurotropes in the blood, at least until the terminal stages of the nervous infection. The pantropic viruses appear more frequently, especially the equine encephalomyelitis—yellow fever—louping-ill group in which a period of blood infection is a characteristic feature of the pre-nervous phases of the disease and allows of transmission of the contagium by blood-sucking insects. From a pathogenetic standpoint the significance of virus in the blood lies not in the immediate consequences, for the normal hæmato-encephalic barrier is probably impervious to most if not all viruses, but in the possible distribution of virus to areas from which the nervous system may be infected. In the case of some pantropic viruses infective visceral foci are thus established from which ascent to the nervous system by the neural route may follow. Other viruses appear on the nasal mucosa and reach the nervous system by the olfactory nerve or, more probably, by its accompanying lymphatics. The possibility of a slow " growth through " the hæmato-encephalic barrier, due to infection of its constituent cells by a virus, must also be considered, though at present there is no certain evidence of such an occurrence.

A Suggested Basis for Classification of Viruses Affecting the Nervous System.

Even though our knowledge is far from complete, it is permissible to attempt a classification of the known facts provided that the possibly temporary nature of the edifice be clearly recognized. Though ultimately modified or discarded, it serves for a time as a framework within which new findings may be more readily compared or contrasted with old. The following purely tentative grouping of the viruses discussed above is suggested.

Group 1. *The stricter neurotropes.*—These attack directly and destroy nerve cells, central and peripheral, but are without obvious direct action on other cells; the inflammatory reaction in the nervous tissues is purely secondary and reactive. They do not multiply except in nervous tissue. Introduced at a peripheral site they pass up the local nerves to the central nervous system; inoculated into a denervated area no disease results. They are rarely found in blood or cerebrospinal fluid, at any rate until late in the nervous disease; intravenous inoculation of moderate to small doses is usually ineffective. Examples are the viruses of poliomyelitis, rabies, pseudorabies (in the monkey), and Borna disease.

Group 2. *The pantropic viruses, Type* 1.—While definitely neurotropic, these also directly attack and produce specific lesions in cells derived from all embryonic layers. In the nervous system, consequently, they attack both ectodermal and mesodermal structures ; in the viscera they may produce multiple foci of necrosis. They grow with greater or less facility in situations outside the nervous system, as well as in the brain and cord. They may or may not be easily detected in the blood ; if not, indirect evidence of blood spread is often forthcoming, but invasion of the nervous system is by way of the peripheral nerves. Inoculation into a denervated area often leads to the nervous disease ; in these cases local growth followed by blood contamination allows the virus to set up infective visceral foci from which follows invasion of the nervous system by the visceral nerves. Intravenous inoculation of small doses is often effective. Examples are the virus of herpes febrilis (in the rabbit, &c.), that of pseudorabies (in the rabbit), and the B. virus ; the herpes virus is probably nearer the stricter neurotropes than are the other two.

Group 3. *The pantropic viruses, Type* 2.—Although these viruses as a group are pantropic, the cellular affinities of individual representatives are more restricted than with viruses of Type 1 ; outside the nervous system they are directed particularly to epithelial and blood-vascular structures. Characteristically, a phase of blood infection is followed by systemic immunity ; in a certain proportion of cases encephalitis supervenes after the virus has disappeared from the blood, and when presumably the body as a whole already is, or is becoming, immune. Intravenous inoculation is often successful with small doses. Many of these diseases are spread in nature by blood-sucking insects. In the case of one of these viruses, that of equine encephalomyelitis, no evidence of neural spread is forthcoming ; during circulation in the blood, virus appears on the nasal mucosa and reaches the brain probably by the perineural lymphatics of the olfactory nerves. Further investigation is needed to show whether such behaviour is typical of the group. In the nervous system there is a primary and direct attack on the nervous elements. Examples are the viruses of equine encephalomyelitis, yellow fever, louping-ill, and vesicular stomatitis.

Group 4. *The viscerotropic viruses.*—For want of a better, this term is applied for the time being to certain viruses which, under conditions of natural infection, are not excitants of encephalitis. The lesions they promote on inoculation directly into the brain are primarily meningeal, and there is no evidence of damage of nerve cells of greater degree than

accompanies any meningitis of corresponding severity. Examples are the viruses of vaccinia, lymphogranuloma inguinale and salivary-gland disease of guinea-pigs.

A Note on the Selective Distribution of Nervous Lesions Due to Certain Viruses.

One of the most fascinating and at the same time difficult problems confronting the neuropathologist is that of the selective localization of certain morbid processes to given regions of the nervous system. Vogt [33, &c.] seeks to account for many examples of such distribution of lesions on his theory of "pathoclisis," which implies a vulnerability of certain nervous elements inherent in their physicochemical structure. While this assumption, which in one sense seeks to explain the unknown in terms of the unknown, is sometimes unavoidable, it must obviously be made with caution, for time may reveal the participation of determinant factors at present obscure and unconnected with the constitution of particular types of cell. The valuable contributions of Spielmeyer and his pupils [4, 27, 28, 32, &c.] have, for instance, emphasized the importance in some cases of the vascular factor in this connection, though Spielmeyer clearly recognized that it is not always or solely operative. In the realm of virus diseases we meet with several examples of a constant or very frequent elective localization of the most severe lesions, and since we know almost nothing of the underlying causes we must not rashly conclude that in all instances these are of the same nature.

In many diseases of the nervous system due to viruses the seat of maximal pathological changes is in large part dependent upon the site of inoculation or on the route of natural entry of the virus. Thus, inoculated intracerebrally into the rabbit, the B. virus gives rise to an encephalomyelitis with generalized hyperæsthesia, salivation, convulsions and speedy exitus as the cardinal clinical features; on the other hand, inoculated intramuscularly or intradermally in the flank or leg it is responsible for an acute ascending myelitis with death delayed for several days, and cerebral involvement is minimal both clinically and pathologically [37, 38]. Again, speaking quite generally of rabies in the monkey, more intense changes are found in the cord after intrasciatic inoculation than after intracerebral, while higher levels suffer more severely under the reverse circumstances [163].

By way of contrast, in poliomyelitis in both man and monkey the anterior horns of the cord show maximal involvement whether the

virus is introduced intranasally, intracerebrally, or intraneurally. In the motor cortex, often the only cortical area to show damage, cellular infiltration occurs in several laminæ, though opinions differ as to whether the Betz cells are or are not electively destroyed [114, 120, 133]; in the brain-stem neither motor nor sensory nuclei are consistently picked out [133]; in the cord destruction is not absolutely limited to the motor cells [114, 133]. It is inaccurate, therefore, to speak of a pure attack on the motor system [133]; nevertheless, in the cord at any rate, it is the motor nerve cells which are predominantly affected. *In the present state of our knowledge* there appears to be no reason for this unless we assume especial vulnerability of these neurons to the infective agent [114].

An analogous occurrence is seen in louping-ill in the monkey. Whereas in the sheep and the mouse some destruction of Purkinje cells is apparent, and in the mouse the granular layer of the cerebellum may also suffer severely, in the monkey an almost complete, elective disappearance of Purkinje cells follows infection by the intracerebral [80, 85], intrasciatic (personal observation), or intranasal route [82]. Lesions are always present in other parts of the brain, but in no one region are they as severe, or present with such constancy, as in the Purkinje-cell layer.

Thirdly, whether introduced into the brain, the cisterna magna or the sciatic nerve, the virus of pseudorabies exerts its chief action in the monkey on certain cortical areas, though within these areas the major incidence is not on a single type of nerve cell and the glia also is specifically involved [140]. More so than in the preceding instances, there seems here to be an elective attack on given areas as areas, without regard to the precise distribution of a particular kind of neuron.

The relative frequency with which Negri bodies are found in the cornu Ammonis, and some other situations [177], in rabies is accepted by many authors as indicative of greater resistance, due to physico-chemical or developmental factors, of the neurons of this part of the brain [170, 174, 175, &c.]; the nerve cells in question are otherwise relatively normal [186], while destruction of nerve cells and neuronophagia occur in parts where Negri bodies are seen less often.

Among themselves nerve cells differ in certain obvious respects, in size and shape, in the form in which their tigroid substance is precipitated by fixatives, in the number of mitochondria in unit volume, and so on; of possibly more fundamental and significant differences in constitution we have at present little information. If, *faute de mieux*,

in relation to the foregoing observations we postulate differences in structure or metabolism of the different types of neuron, we must not forget that the existence of such differences is largely hypothetical and must remain so until biochemistry can show in just what respect a motor differs from a sensory neuron. It is interesting, however, to note the analogy of the apparent affinity of some viruses for a particular kind of nerve cell to the extraordinarily specific action on a single type of cell of some of the fowl-tumour viruses, or again to the intimate relation between chemical structure in various phenol esters and their remarkably selective action on certain nervous structures [19].

There is one more problem of localization to be mentioned. While it would be far from exact to state that the symptomatology of different diseases due to neurotropic viruses in the smaller laboratory animals is indistinguishable except on the basis of acuteness or otherwise, it is a fact, comprehensible in view of the lesser complexity of the brains of these creatures, that in them the clinical pictures of the various infections are less characteristic than in the higher mammals. As an example, louping-ill and yellow fever induce not dissimilar syndromes in the mouse, differing rather in duration than in the symptoms exhibited. On the contrary, in the monkey the clinical manifestations of the various virus diseases studied by the writer have been highly distinctive and could not readily be confused one with another. Since symptoms reflect merely the localization of lesions, in the lower animals we should anticipate less diverse distribution of the major pathological changes.

Experience has shown that in a number of neurotropic virus diseases of the mouse, guinea-pig and rabbit the outstanding lesion is often massive acute necrosis in the cornu Ammonis and in the rhinencephalic cortex ventral to the *fissura rhinica*; large stretches of pyramidal cells may here be destroyed *in toto*. Lentz first described the eosinophilic, shrunken nerve cells with their pyknotic and fragmented nuclei as characteristic of passage rabies and called them "Passagewutkörperchen" [169], though they had been seen previously by Achúcarro [148], and have, apparently, been re-discovered by Levaditi and his colleagues [169·5]; they occur also in rabbits infected with street virus [163]. Similar appearances obtain in mice with louping-ill [85], yellow fever and St. Louis encephalitis [200], in rabbits with herpetic and virus III infections [212], and in guinea-pigs with equine encephalomyelitis [55]. In the corresponding diseases of higher animals, as the dog, cow, horse, monkey, although foci of destruction of nerve cells may be observed in these situations, the writer has so far not seen massive necrosis of the

kind under consideration; only in pseudorabies in the monkey is the cornu Ammonis affected almost as a whole, and then as only part of the elective distribution of lesions already mentioned. This phenomenon, common to the action of many viruses, is evidently of a different order from the apparently specific affinity between one virus and a given cell system, as in poliomyelitis. It must be regarded not so much as the outcome of a particular virus—host reaction, as the general response of a certain type of host to neurotropic viruses in general. The type of host appears to be that in which the olfactory brain is, relatively speaking, most highly developed, and is presumably relatively more abundantly supplied with fibre connections from other centres. On a previous occasion [55], the opinion was expressed that if the neurotropic viruses spread along axis cylinders we may offer an explanation in terms of the probable amount of virus reaching the affected areas. It has since appeared unlikely that, of those mentioned above, the virus of equine encephalomyelitis is transmitted by the axis cylinders [56]; nevertheless, as we have seen, after intranasal inoculation, or what in many cases amounts to the same thing after intramuscular or subcutaneous inoculation, the distribution of lesions in the brain at an early stage of infection is governed in large part by the central connections of the olfactory nerves. Whatever the correct explanation, it is obvious that this problem of localization of morbid changes is wholly different from that in poliomyelitis and louping-ill.

REFERENCES.

General References and Reviews.

[1] Abel, J. J. *Science*, 1934, **79**, 63 and 121.

[2] Abel, J. J., Evans, E. A., Hampil, B., and Lee, F. C. *Bull. Johns Hopkins Hosp.*, 1935, **56**, 84.

[3] André, J. M. "Contribution à l'étude des Lymphatiques du Nez et des Fosses Nasales." Paris. 1905.

[4] Bodechtel, G. *Zeit. f. d. ges. Neurol. u. Psychiatr.*, 1930, **123**, 485.

[5] Boemke, F. *Virch. Arch. f. path. Anat.*, 1934, **293**, 180.

[6] Carmichael, E. A. *Journ. Neurol. and Psychopath.*, 1929, **9**, 209.

[7] Clark, W. E. le Gros. Reports on Public Health, No. 54. H.M. Stationery Office, London. 1928.

[8] Cowdry, E. V. *Arch. Path.*, 1934, **18**, 527.

[8·5] Demme, H. *Deut. Zeit. f. Nervenheilk.*, 1933, **130**, 88.

[9] De Renyi, G. S. In "Special Cytology." Edited by E. V. Cowdry, vol. 3, p. 1370. New York. 1932.

[10] Elman, R. *Bull. Johns Hopkins Hosp.*, 1923, **34**, 99.

[11] Friedemann, U., and Elkeles, A. *Lancet*, 1934 (i), 719, 775.

[12] Horster, H., and Whitman, L. *Zeit. f. Hyg. u. Infektionskr.*, 1932, **113**, 113.

[12·5] Klieneberger, E. *Arch. f. exp. Path. u. Pharmakol.*, 1931, **161**, 485.

[13] Le Fèvre de Arric, M., and Millet, M. *C.R. Soc. Biol.*, 1925, **93**, 45.
[14] *Idem. Ibid.*, 1926, **94**, 782.
[15] *Idem. Ibid.*, 1927, **96**, 206.
[16] Levaditi, C. *C.R. Soc. Biol.*, 1921, **85**, 425.
[17] *Idem. Ann. Inst. Past.*, 1930, **45**, 673.
[18] Levaditi, C., Lépine, P., and Schoen, R. *Ibid.*, 1929, **43**, 1465.
[19] Lillie, R. D., and Smith, M. I. National Inst. of Health, Bull. 160. U.S. Treasury Dept., Washington. 1932.
[20] Marinesco, G., and Draganesco, S. *Rev. Neurol.*, 1932 (i), 1.
[21] McKinley, E., and Holden, M. *Proc. Soc. Exp. Biol. and Med.*, 1927, **24**, 595.
[22] Nicolau, S., Nicolau, O., and Galloway, I. A. *Ann. Inst. Past.*, 1929, **43**, 1.
[23] Philibert, A. *Ann. Med.*, 1924, **16**, 283.
[24] Rivers, T. M. *Amer. Journ. Path.*, 1928, **4**, 91.
[25] Seifried, O. *Ergeb. allg. Path. u. path. Anat.*, 1931, **24**, 554.
[26] Seifried, O., and Spatz, H. *Zeit. f. d. ges. Neurol. u. Psychiatr*, 1930, **124**, 317.
[27] Spielmeyer, W. *Ibid.*, 1925, **99**, 756.
[28] *Idem. Ibid.*, 1928, **118**, 1.
[28·5] Sullivan, W. E., and Mortensen, O. A. *Anat. Rec.*, 1934, **59**, 493.
[29] Thiele, F. H., and Embleton, D. *Proc. Roy. Soc. Med.*, 1914, **7**, Path. Sect., 68.
[30] Turner, A. L., and Reynolds, F. E. *Journ. Laryngol. and Otol.*, 1926, **41**, 717.
[31] *Idem. Ibid.*, 1927, **42**, 525.
[32] Uchimura, J. *Zeit. f. d. ges. Neurol. u. Psychiatr.*, 1928, **112**, 1.
[33] Vogt, O. *Journ. f. Psych. u. Neurol.*, 1925, **31**, 245.
[34] Weed, L. H. *Journ. Med. Res.*, 1914, **31**, 21.
[35] Yuien, K. *Fol. Anat. Jap.*, 1928, **6**, 301.

B. Virus.

[36] Sabin, A. B. *Brit. Journ. Exp. Path.*, 1934, **15**, 268.
[37] Sabin, A. B., and Hurst, E. W. *Ibid.*, 1935, **16**, 133.
[38] Sabin, A. B., and Wright, A. M. *Journ. Exp. Med.*, 1934, **59**, 115.

Borna Disease.

[39] Ernst, W., and Hahn, H. *Münch. tierärtz. Wchnschr.*, 1927, **78**, 85.
[40] Nicolau, S., and Galloway, I. A. Medical Research Council Report, No. 121, H.M. Stationery Office, London. 1928.
[41] Nicolau, S., Galloway, I. A., and Nicolau, O. *C. R. Soc. Biol.*, 1928, **99**, 674.
[42] Zwick, W., Seifried, O., and Witte, J. *Zeit. f. Infektionskr. Haust.*, 1927, **30**, 42.
[43] *Idem. Arch. f. wiss. u. prakt. Tierheilk.*, 1929, **59**, 511.

Dog Distemper.

[44] Babes, V., and Starcovici, C. *C. R. Soc. Biol.*, 1912, **73**, 229.
[45] Cerletti, U. *Zeit. f. d. ges. Neurol. u. Psychiatr.*, 1912, **9**, 520.
[46] Dunkin, G. W., and Laidlaw, P. P. *Journ. Comp. Path. and Therap.*, 1926, **39**, 201, 213.
[47] Gallego, A. *Zeit. f. Infektionskr. Haust.*, 1928, **34**, 38.
[48] Marinesco, G., Draganesco, S., and Stroesco, G. *Ann. Inst. Past.*, 1933, **51**, 215.
[49] Perdrau, J. R., and Pugh, L. P. *Journ. Path. and Bact.*, 1930, **33**, 79.
[50] Sanfelice, F. *Cent. Bakt.*, Abt. 1, Orig., 1915, **76**, 495.

Epizootic Fox Encephalitis.

[51] Green, R. G., Katter, M. S., Shillinger, J. E., and Hanson, K. B. *Amer. Journ. Hyg.*, 1933, **18**, 462.
[52] Green, R. G., Ziegler, N. R., Carlson, W. E., Shillinger, J. E., Tyler, S. H., and Dewey, E. T. *Ibid.*, 1934, **19**, 343.
[53] Green, R. G., and Shillinger, J. E. *Ibid.*, 1934, **19**, 362.
[54] Levaditi, C., Lépine, P., Bazin, J., and Schoen, R. *C. R. Soc. Biol.*, 1930, **104** 755.

EQUINE ENCEPHALOMYELITIS.

[55] HURST, E. W. *Journ. Exp. Med.*, 1934, **59**, 529.
[56] *Idem. Journ. Path. and Bact.*, 1936, **42**, 271.
[57] KELSER, R. A. *Journ. Amer. Vet. Med. Assoc.*, 1933, **82**, 767.
[58] MERRILL, M. H., LACAILLADE, C. W., and TENBROECK, C. *Science*, 1934, **80**, 251.
[58·5] MERRILL, M. H., and TENBROECK, C. *Journ. Exp. Med.*, 1935, **62**, 687.

HERPES FEBRILIS.

[59] DA FANO, C. *Journ. Path. and Bact.*, 1923, **26**, 85.
[60] DA FANO, C., and PERDRAU, J. R. *Ibid.*, 1927, **30**, 67.
[61] DOERR, R., and VÖCHTING, R. *Rev. gen. Ophth.*, 1920, **34**, 409.
[62] FLEXNER, S., and AMOSS, H. L. *Journ. Exp. Med.*, 1925, **41**, 215.
[63] *Idem. Ibid.*, 1925, **41**, 357.
[64] GOODPASTURE, E. W. *Amer. Journ. Path.*, 1925, **1**, 1.
[65] *Idem. Ibid.*, 1925, **1**, 11.
[66] GOODPASTURE, E. W., and TEAGUE, O. *Journ. Med. Res.*, 1923, **44**, 121.
[67] *Idem. Ibid.*, 1923, **44**, 139.
[68] KOPPISCH, E. *Zeit. f. Hyg. u. Infektionskr.*, 1935, **117**, 386.
[69] LEVADITI, C. *L'Herpès et le Zona*, Paris, 1926.
[70] MARINESCO, G., and DRAGANESCO, S. *Ann. Inst. Past.*, 1923, **37**, 753.
[71] PETTE, H. *Verhandl. d. Gesellsch. deut. Nervenärzte*, 1926, 207.
[72] *Idem. Deut. Zeit. f. Nervenheilk.*, 1931, **121**, 113, 143; **122**, 209, 221.
[73] REMLINGER, P., and BAILLY, J. *C. R. Soc. Biol.*, 1925, **93**, 1071.
[74] ROSE, G., and WALTHARD, B. *Zeit. f. Hyg. u. Infektionskr.*, 1926, **105**, 645.
[75] SMITH, W. *Journ. Path. and Bact.*, 1931, **34**, 493.
[76] *Idem. Ibid.*, 1931, **34**, 747.

HOG CHOLERA.

[77] SEIFRIED, O. *Journ. Exp. Med.*, 1931, **53**, 277.
[78] SEIFRIED, O., and CAIN, C. B. *Ibid.*, 1932, **56**, 345, 351.

LOUPING-ILL.

[79] BROWNLEE, A., and WILSON, D. R. *Journ. Comp. Path. and Therap.*, 1932, **45**, 67.
[80] FINDLAY, G. M. *Brit. Journ. Exp. Path.*, 1932, **13**, 230.
[81] FITE, G. L., and WEBSTER, L. T. *Proc. Soc. Exp. Biol. and Med.*, 1934, **31**, 695.
[82] GALLOWAY, I. A., and PERDRAU, J. R. *Journ. Hyg.*, 1935, **35**, 339.
[83] GORDON, W. S. *Brit. Med. Journ.*, 1934 (**i**), 885.
[84] GORDON, W. S., BROWNLEE, A., WILSON, D. R., and MACLEOD, J. *Journ. Comp. Path. and Therap.*, 1932, **45**, 106.
[85] HURST, E. W. *Ibid.*, 1931, **44**, 231.
[86] MACLEOD, J., and GORDON, W. S. *Ibid.*, 1932, **45**, 240.
[87] POOL, W. A., BROWNLEE, A., and WILSON, D. R. *Ibid.*, 1930, **43**, 253.

LYMPHOCYTIC CHORIOMENINGITIS.

[88] ARMSTRONG, C., and DICKENS, F. Pub. Health Rep., U.S. Treasury Dept., 1935, **50**, 831.
[89] ARMSTRONG, C., and LILLIE, R. D. *Ibid.*, 1934, **49**, 1019.
[90] ARMSTRONG, C., and WOOLEY, J. G. *Ibid.*, 1935, **50**, 537.
[91] RIVERS, T. M., and MCNAIR SCOTT, T. F. *Science*, 1935, **81**, 439.
[92] TRAUB, E. *Science*, 1935, **81**, 298.

LYMPHOGRANULOMA INGUINALE.

[93] D'AUNOY, R., HAAM, E. VON, and LICHTENSTEIN, L. *Amer. Journ. Path.*, 1935, **11**, 737.
[94] FINDLAY, G. M. *Lancet*, 1932, (**ii**), 11.
[95] *Idem. Trans. Roy. Soc. Med. and Hyg.*, 1933, **27**, 35.
[96] HELLERSTRÖM, S., and WASSÉN, E. Memorial Volume to Prof. J. Cantacuzène, Paris, 1934, 277.

[97] Jonesco-Mihaiesti, C., Tupa, A., Badenski, G., and Wismer, B. *Bull. Acad. Med.*, 1933, **109**, 652.
[98] Levaditi, C., Ravaut, P., Lépine, P., and Schoen, R. *Ann. Inst. Past.*, 1932, **48**, 27.
[99] Levaditi, C. *Bull. Acad. Med.*, 1933, **109**, 684.

Poliomyelitis.

[100] Abramson, H. L. *Journ. Amer. Med. Assoc.*, 1917, **68**, 546.
[101] *Idem. Arch. Int. Med.*, 1918, **22**, 312.
[102] Amoss, H. L. "In Filterable Viruses." edited by T. M. Rivers. Baltimore. 1928.
[103] André-Thomas and Lhermitte, J. *Rev. Neurol.*, 1929, **36** (i), 1242.
[104] Blanton, W. B. *Journ. Med. Res.*, 1917, **36**, 1.
[105] Brodie, M. Cited in "Poliomyelitis," International Committee for the Study of Infantile Paralysis. Baltimore, 1932, p. 290.
[106] Brodie, M., and Elvidge, A. R. *Science*, 1934, **79**, 234.
[107] Clark, P. F., Fraser, F. R., and Amoss, H. L. *Journ. Exp. Med.*, 1914, **19**, 223.
[108] Faber, H. K., and Gebhardt, L. P. *Ibid.*, 1933, **57**, 933.
[109] Fairbrother, R. W., and Hurst, E. W. *Journ. Path. and Bact.*, 1930, **33**, 17.
[110] Flexner, S., and Amoss, H. L. *Journ. Exp. Med.*, 1914, **20**, 249.
[111] *Idem. Ibid.*, 1917, **25**, 525.
[112] Flexner, S., and Clark, P. F. *Journ. Amer. Med. Assoc.*, 1911, **57**, 1685.
[113] Howe, H. S. *Journ. Nerv. and Ment. Dis.*, 1918, **48**, 97 and 206; **50**, 409.
[114] Hurst, E. W. *Journ. Path. and Bact.*, 1929, **32**, 457.
[115] *Idem. Ibid.*, 1930, **33**, 1133.
[116] *Idem. Ibid.*, 1932, **35**, 41.
[117] *Idem.* Cited in "Poliomyelitis," International Committee for the Study of Infantile Paralysis. Baltimore, 1932, p. 299.
[118] Jungeblut, C. W. Cited in "Poliomyelitis," International Committee for the Study of Infantile Paralysis. Baltimore, 1932, p. 82.
[119] Jungeblut, C. W., and Spring, W. J. *Proc. Soc. Exp. Biol. and Med.*, 1930, **27**, 1076
[120] Környey, St. *Zeit. f. d. ges. Neurol. u. Psychiatr.*, 1933, **146**, 724.
[121] Landsteiner, K., and Levaditi, C. *Ann. Inst. Past.*, 1910, **24**, 833.
[122] Landsteiner, K., Levaditi, C., and Pastia, M. *Ibid.*, 1911, **25**, 804.
[123] Leiner, C., and von Wiesner, R. *Wien. klin. Woch.*, 1909, **22**, 1698.
[124] Lennette, E. H., and Hudson, N. P. *Proc. Soc. Exp. Biol. and Med.*, 1935, **32**, 1444.
[125] Marinesco, G. *C.R. Soc. Biol.*, 1911, **70**, 286.
[126] O'Leary, J. L., Heinbecker, P., and Bishop, G. H. *Arch. Neurol. and Psychiatr.*, 1932, **28**, 272.
[127] Olitsky, P. K., Rhoads, C. P., and Long, P. H. *Journ. Amer. Med. Assoc.*, 1929, **92**, 1725.
[128] Pette, H. *Deut. Zeit. f. Nervenheilk.*, 1930, **116**.
[129] Pette, H., Demme, H., and Környey, St. *Ibid.*, 1932, **128**, 125.
[130] Rissler, J. *Nord. med. Arkiv*, 1888, **20**, 1.
[131] Römer, P. H. "Die epidemische Kinderlähmung." Berlin. 1911.
[132] Schultz, E. W., and Gebhardt, L. P. *Proc. Soc. Exp. Biol. and Med.*, 1933, **31**, 728.
[133] Spielmeyer, W. *Zeit. f. d. ges. Neurol. u. Psychiatr.*, 1932, **142**, 159.
[134] Warburg, B. *Arch. Neurol. and Psychiatr.*, 1931, **25**, 1191.
[135] Wickman, I. "Die akute Poliomyelitis bzw. Heine-Medinische Krankheit." Berlin. 1911.
[136] Zappert, J., von Wiesner, R., and Leiner, K. "Studien über die Heine-Medinische Krankheit." Leipzig u. Wien. 1911.

Pseudorabies.

[137] Aujeszky, A. *Cent. Bakt.*, Abt. 1, Orig., 1902, **32**, 353.
[138] Hurst, E. W. *Journ. Exp. Med.*, 1933, **58**, 415.
[139] *Idem. Ibid.*, 1934, **59**, 729.
[140] *Idem. Ibid.*, 1936. To appear in March number.

[141] Isabolinsky, M., and Patzewitsch, B. *Cent. Bakt.*, Abt. 1, Orig., 1912, **65**, 256.
[142] Remlinger, P., and Bailly, J. *C.R. Soc. Biol.*, 1933, **113**, 125.
[143] Sangiorgi, G. *Pathologica*, 1914, **6**, 282.
[144] Schmiedhoffer, J. *Zeit. f. Infektionskr. Haust.*, 1910, **8**, 383.
[145] Shope, R. E. *Journ. Exp. Med.*, 1931, **54**, 233.
[146] *Idem. Proc. Soc. Exp. Biol. and Med.*, 1932, **30**, 308.
[147] Zwick, and Zeller. *Arb. a. d. Kaiserlich. Gesundheits*, 1911, **36**, 382.

Rabies.

[148] Achúcarro, N. *Nissl. u. Alzheimer's Arb.*, 1910, **3**, 143.
[149] Babes, V. *Ann. Inst. Past.*, 1892, **6**, 209.
[150] *Idem.* "Traité de la Rage." Paris. 1912.
[151] Bertarelli, E. *Cent. Bakt.*, Abt. 1, Orig., 1904, **37**, 213.
[152] Dawydowski, J. V., and Dwijkoff, P. P. *Verhandl. deut. path. Gesellsch.*, 1928, **23**, 427.
[153] Di Vestea, A., and Zagari, G. *Ann. Inst. Past.*, 1887, **1**, 492.
[154] *Idem. Ibid.*, 1889, **3**, 237.
[155] Duboué. "De la physiologie pathologique et du traitement rationnel de la rage." Paris. 1879. (Cited by Gamaleia.)
[156] Fedoroff, H. *Zeit. f. d. ges. Neurol. u. Psychiatr.*, 1925, **100**, 248.
[157] Fermi, C. *Cent. Bakt.*, Abt. 1, Orig., 1907, **44**, 25.
[158] Gamaleia. *Ann. Inst. Past.*, 1887, **1**, 63.
[159] Gannt, W. H., and Ponomarew, A. W. *Zeit. f. d. ges. exp. Med.*, 1929, **66**, 582.
[160] Goodpasture, E. W. *Amer. Journ. Path.*, 1925, **1**, 547.
[161] Helman, M. C. *Ann. Inst. Past.*, 1889, **3**, 15.
[162] Herrmann, O. *Cent. Bakt.*, Abt. 1, Orig., 1925, **95**, 429.
[163] Hurst, E. W., and Pawan, J. L. *Journ. Path. and Bact.*, 1932, **35**, 301.
[164] Jowelew, B. M. *Zeit. f. d. ges. exp. Med.*, 1930, **74**, 217.
[165] Kerbler, F. *Zeit. f. Hyg. u. Infektionskr.*, 1933, **115**, 235.
[166] Klarfeld, B. *Zeit. f. d. ges. Neurol. u. Psychiatr.*, 1922, **77**, 80.
[167] Konradi, D. *Cent. Bakt.*, Abt. 1, Orig., 1922, **88**, 113.
[168] Krinitzky, S. I. *Virch. Arch. f. path. Anat.*, 1926, **261**, 802.
[169] Lentz, O. *Zeit. f. Hyg. u. Infektionskr.*, 1909, **62**, 63.
[169·5] Levaditi, C., Lépine, P., and Schoen, R. *C. R. Soc. Biol.*, 1929, **101**, 1050.
[170] Levaditi, C., Nicolau, S., and Schoen, R. *Ann. Inst. Past.*, 1926, **40**, 973.
[171] Levaditi, C., and Schoen, R. *C. R. Soc. Biol.*, 1933, **114**, 501.
[172] Lowenberg, K. *Arch. Neurol. and Psychiatr.*, 1928, **19**, 638.
[173] Manouelian, Y., and Viala, J. *C. R. Acad. Sci.*, 1928, **186**, 1242.
[174] *Idem. Ibid.*, 1928, **187**, 1168.
[175] Marinesco, G., and Stroesco, G. *Arch. Roum. Path. Exp.*, 1931, **4**, 243.
[176] Marinesco, G., and Draganesco, S., *Ann. Inst. Past.*, 1935, **54**, 299.
[177] Nicolau, S., and Kopciowska, L. *C. R. Acad. Sci.*, 1932, **194**, 1865.
[178] Nicolau, S., and Mateiesco, E. *Ibid.*, 1928, **186**, 1072.
[179] Nicolau, S., and Serbanescu, V. *C. R. Soc. Biol.*, 1928, **99**, 294.
[180] Repetto, R. *Cent. Bakt.*, Abt. 1, Orig., 1909, **49**, 457.
[181] Riesman, D., Fox, W. W., Alpers, B. J., and Cooper, D. A. *Arch. Int. Med.*, 1933, **51**, 644.
[182] Rojas, L. *Arch. f. Psychiatr.*, 1932, **96**, 1.
[183] Rous, E. *Ann. Inst. Past.*, 1889, **3**, 69.
[184] Schaffer, K. *Ibid.*, 1889, **3**, 644.
[185] *Idem. Zeit. f. d. ges. Neurol. u. Psychiatr.*, 1931, **136**, 547.
[186] Schiffman, J. *Zeit. f. Hyg. u. Infektionskr.*, 1906, **52**, 199.
[187] Schukri, L., and Spatz, H. *Zeit. f. d. ges. Neurol. u. Psychiatr.*, 1925, **97**, 627.
[188] Schweinburg, F. *Zent. Bakt.*, Abt. 1, Orig., 1932, **124**, 426.
[189] Schweinburg, F., and Windholz, F. *Virch. Arch. f. path. Anat.*, 1930, **278**, 23.

190] Slotwer, B. S. *Ibid.*, 1926, **261**, 787.
[191] Speransky, A. *Ann. Inst. Past.*, 1927, **41**, 166.
[192] Standfuss, R. *Arch. f. wiss. u. prakt. Tierheilk.*, 1908. **34**, 109.

Salivary Gland Virus of Guinea-Pigs.

[193] Andrewes, C. H. *Brit. Journ. Exp. Path.*, 1930, **11**, 23.
[194] Cole, R., and Kuttner, A. G. *Journ. Exp. Med.*, 1926, **44**, 855.
[195] Hudson, N. P., and Markham, F. S. *Ibid.*, 1932, **55**, 405.
[195·5] Kuttner, A. G., and T'ung, T. *Ibid.*, 1935, **62**, 805.

St. Louis Encephalitis.

[196] McCordock, H. A., Collier, W., and Gray, S. H. *Journ. Amer. Med. Assoc.*, 1934, **103**, 822.
[197] Muckenfuss, R. S., Armstrong, C., and Webster, L. T. *Ibid.*, 1934, **103**, 731.
[198] Smadel, J. E., and Moore, E. *Amer. Journ. Path.*, 1934, **10**, 827.
[199] Webster, L. T., and Fite, G. L. *Science*, 1933, **78**, 463.
[200] *Idem. Journ. Exp. Med.*, 1935, **61**, 103.

Vaccinia.

[201] Douglas, S. R., Smith, W., and Price, L. R. W. *Journ. Path. and Bact.*, 1929, **32**, 99.
[202] Gildemeister, E., and Hilgers, P. *Deut. med. Wchnschr.*, 1930, **56**, 312.
[203] Hurst, E. W., and Fairbrother, R. W. *Journ. Path. and Bact*, 1930, **33**, 463.
[204] Levaditi, C., and Nicolau, S. *Ann. Inst. Past.*, 1923, **37**, 1.
[205] Levaditi, C., Nicolau, S., and Sanchis Bayarri, V. *Presse méd.*, 1927, **35**, 161.
[206] Ohtawara, T. Sci. Rep. Gov. Inst. Infect. Dis., Tokyo, 1922, **1**, 203.
[207] Pette, H., and Környey, St. *Zeit. f. Hyg. u. Infektionskr.*, 1933, **115**, 752.
[208] Rivers, T. M., Sprunt, D. H., and Berry, G. P. *Journ. Exp. Med.*, 1933, **58**, 39.
[209] Winkler, W. F. *Arch. f. Hyg.*, 1927, **98**. 241.
[210] *Idem. Zeit. f. Immunitätsforsch.*, 1931, **73**, 185.

Virus III.

[211] Miller, C. P., Andrewes, C. H., and Swift, H. F. *Journ. Exp. Med.*, 1924, **40**, 773.
[212] Rivers, T. M., and Stewart, F. W. *Ibid.*, 1928, **48**, 603.
[213] Rivers, T. M., and Tillett, W. S. *Ibid.*, 1924, **40**, 281.

Yellow Fever.

[214] Dinger, J. E. *Zent. Bakt.*, Abt. 1, Orig., 1931, **121**, 194.
[215] Findlay, G. M., and Clarke, L. P. *Journ. Path. and Bact.*, 1935, **40**, 55.
[216] *Idem. Trans. Roy. Soc. Trop. Med. and Hyg.*, 1935, **28**, 579.
[217] Findlay, G. M., and Stern, R. O. *Journ. Path. and Bact.*, 1935, **40**, 311.
[217·5] *Idem. Ibid.*, 1935, **41**, 431.
[218] Goodpasture, E. W. *Amer. Journ. Path.*, 1932, **8**, 137.
[219] Hughes, T. P., and Theiler, M. *Journ. Bact.*, 1934, **27**, 76.
[220] Lloyd, W., and Penna, H. A. *Amer. Journ. Trop. Med.*, 1933, **13**, 1.
[221] Nicolau, S., Kopciowska, L., and Mathis, M. *Ann. Inst. Past.*, 1934, **53**, 455.
[222] Theiler, M. *Ann. Trop. Med.*, 1930, **24**, 249.
[223] *Idem. Amer. Journ. Trop. Med.*, 1933. **13**, 399.
[224] Theiler, M., and Hughes, T. P. *Trans. Roy. Soc. Trop. Med. and Hyg.*, 1935, **28**, 481.

THE EFFECTS OF OCCIPITAL LOBECTOMY ON VISION IN CHIMPANZEE.

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INTRODUCTION.

IT has long been known that central vision appears to suffer relatively less than peripheral vision following unilateral destruction of the occipital cortex. Indeed, when the striata area is subtotally removed in man, central or macular vision may be more or less completely preserved, the deficit being confined to the peripheral, homonymous fields of the side opposite to the lesion. However, other cases, and they are generally those involving larger lesions, show a complete homonymous hemianopsia of the opposite side including the macular portion of the fields, with the vertical line passing through the points of fixation. For the most part the clinical examination of these cases of injury to the occipital lobe have consisted of field determinations by perimetric methods, and, in a few instances, visual acuity measurements. These latter, however, usually have been made with relatively crude methods and, therefore, have been of little value in interpreting the relation of the visual cortical centres to this function. A further limitation is the fact that the normal visual acuity of the subject, i.e. antedating the pathological condition, is not usually known.

An opportunity to study the effects of occipital lobectomy upon visual acuity in chimpanzee was recently presented to us. The subject of the experiment, a co-operative adolescent female chimpanzee, had been used extensively over a period of two years in a comparative study of human and chimpanzee vision [15], during which stable acuity standards had been established over a medium brightness range. As it was not desired to use this subject for breeding purposes in the Laboratories of Primate Biology it was decided do utilize it in a terminal experiment on the effects of cortical injury upon visual acuity.

Two successive cortical extirpations were made. At the first

operation the entire left occipital lobe, including all calcarine cortex, was removed. Visual acuity determinations at four brightness levels were made between the seventh and forty-third day after operation. A second operation involving subtotal extirpation of the right occipital lobe was then performed and visual acuity again tested. An attempt was also made to determine the limits of the fields of vision following each operation. This is the first recorded study of the results of occipital lobectomy in a chimpanzee.

Apparatus and Methods for Measuring Visual Acuity.

Apparatus.—The apparatus employed in measuring visual acuity was the Ives Visual Acuity Test Object[1] [8]. This instrument presents to the subject an illuminated circular field, 7 cm. in diameter, containing black and white striæ equal in width. These striæ, which are produced by the rotation about each other of two glass plates on which are ruled very fine opaque lines, 240 to the inch, may be varied reciprocally as to size and number, increasing in number and decreasing in size as the angle formed by rotating the two sets of grating lines is made larger. When the striæ are very small and viewed at a sufficiently great distance they cannot be resolved by the eye and the test field appears as a circular form of homogenous brightness. Total brightness of the test field remains constant for all sizes of the stimulus bands.

Visual acuity is determined with this instrument by ascertaining the smallest width of stimulus lines that can be resolved by the eye, i.e. that permits the test field being perceived as containing distinct lines and not being of homogeneous brightness. Visual acuity is measured in terms of the angle subtended at the eye by this minimal (threshold) width of the stimulus lines.

A modification of the Yerkes-Watson discrimination apparatus [17] was used in the training. It consisted of an experimental cage, the front wall of which was solid except for two openings, a lower one through which the animal could extend its hands to food boxes and a small upper one ($2\frac{1}{2}$ by $4\frac{1}{2}$ in.) at the level of the test objects which provided a window through which the animal could look at them. A single, sliding panel, operated by the experimenter, opened and closed both of these openings simultaneously. The relations of the stimulus

[1] One of the two instruments used in the present investigation was originally designed and constructed by Dr. H. E. Ives of the Bell Telephone Laboratories as a model for Bausch and Lomb Company. A duplicate of this instrument was made in the shop of the Physics Laboratory of Yale University. The glass gratings were obtained at Max Levy and Company, Philadelphia.

objects to the food-boxes is shown in fig. 1. The food-boxes (F_1 F_2), which were contained in a long box (H), were directly below and in front of the two Ives test objects (G_1 G_2), each of which was fastened to the front of a light box. The food box was placed at slightly less than arm's length from the animal's cage. All parts of the apparatus were painted a flat black and were located in a room from which all outside light was excluded. Further details of the apparatus, controls of

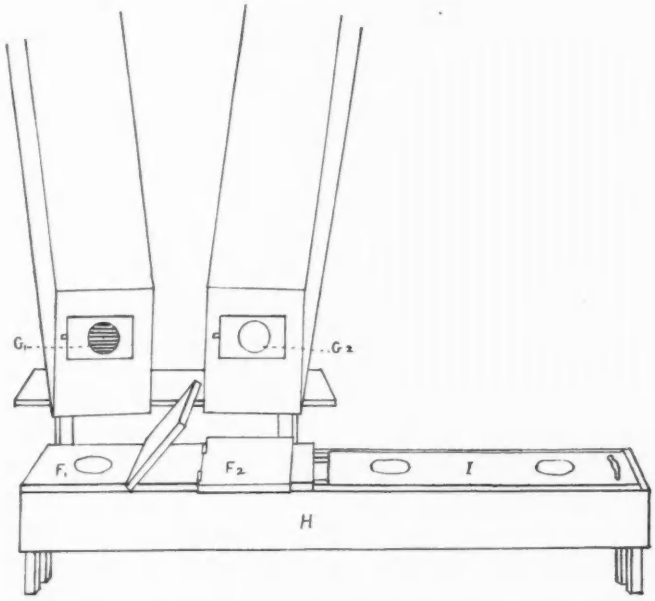

FIG. 1.—Showing the relation of the Stimuli to the Food Boxes. *F, F,* Location of food cups; *G, G,* Ives visual acuity test objects; *H,* food box; *I,* sliding panel into which food cups fitted.

secondary cues, and measurement of light sources, are described elsewhere [15].

Experimental procedure.—In the preliminary training the animal was taught that when the sliding panel was raised it was to look through the small window thus exposed and, after observing on which side the circular field containing white and black striae was located, to reach through the lower opening and obtain food from the food box on the corresponding side. If the wrong box was chosen, i.e. the one on the side corresponding to the clear test field, the animal received no reward

and was required to withdraw its hand and await another trial, usually given within thirty to forty-five seconds. The positions of the correct and incorrect stimulus fields were varied from left to right according to a chance series with the restriction that the same stimulus was never on one side more than three times in succession.

Once the animal had learned to discriminate so that it was responding without error, i.e. always choosing the stimulus with the lines, determination of thresholds for the perception of the lines was begun. Beginning with stimulus lines that were readily perceived by the animal, the width of the striae was reduced every five trials until the discrimination broke down. The width of the lines was then increased to a value which the animal was well able to discriminate correctly and the procedure repeated until reliable thresholds were obtained. The number of such series of descents varied with the brightnesses and distances of the stimuli.

In the pre-operative tests the animal was used once or twice daily, the number of trials in a given experimental period varying with the degree of motivation. Usually the subject worked from 20 to 35 trials, occasionally as many as 50. A ten-minute period of dark adaptation preceded each experimental series so that when the threshold regions were reached the period of darkness adaptation was at least twenty minutes. The procedure in post-operative tests was essentially the same except that experimentation was limited to one period per day.

Surgical Procedures and Post-operative Recovery.

First operation (*May* 24, 1933). *Extirpation of the left occipital lobe* (*Area striata*). (*Drs. J. F. Fulton, D. G. Marquis and J. W. Watts.*[1])—Under fairly deep sodium-amytal anæsthesia (20·5 c.c. 10 per cent. solution, injected intra-peritoneally) a large, posteriorly situated, left-sided bone-flap was turned back, the dura opened, and a cellophane tracing and free-hand sketch made of the chief sulci. The extirpation was carried out with the Davis-Bovie electro-surgical unit. After first coagulating the large blood-vessels surrounding the area, the cortex along the occipital sulcus was incised. The remaining part of the dissection was carried out with blunt spatulas, the tissue being removed in a single piece. The extirpated block weighed 18 grm. and included all tissue posterior to the parieto-occipital sulcus and the entire cerebellar surface of the hemisphere up to within about 5 mm. of the corpus

[1] The writers wish to acknowledge the assistance of Drs. C. F. Jacobsen, R. U. Light, D. G. Marquis, and J. W. Watts.

callosum; all cortical tissue in the region of the calcarine fissure up to the corpus callosum was then sucked away. Subsequent examination of the brain by Poliak and Rei Hayashi [14] revealed that the excision of the area striata was complete. The dura was reapproximated with silk sutures and the bone-flap replaced in the usual manner.

Post-operative notes.—Same day: Examination about three hours after completion of operation showed eyes opened and deviated conjugately to the left.

First day: The eyes were deviated to the left but were capable of extreme deviation to the right. The right pupil seemed slightly larger than the left. Gross examination revealed right homonymous hemianopsia.

Second day: The animal moved around her quarters more freely. Although movements were executed slowly there was no indication of motor impairment of the limbs. Eye movements were made with facility in all directions and the pupillary response to light was normal. Detail vision was apparently good, for the animal was able to see and pick up with accuracy small pieces of banana from the floor.

Third day: An examination of the visual fields revealed a right homonymous hemianopsia. When a moving object was passed from right to left in the field of vision, the eyes invariably jumped and were fixated only when the object had reached the mid-line. The conjugate twitching as the object comes into the field of vision was much more marked than is the corresponding phenomenon in a human being. The pupils were approximately equal and eye movements were in all directions. The tendency towards involuntary deviation of the eyes to the left had more or less disappeared. Tests of visual acuity were undertaken after the seventh post-operative day (see below).

Second operation (*July* 7, 1933). *Subtotal extirpation of the right occipital lobe.* (*Drs. J. F. Fulton, R. U. Light and D. G. Marquis.*)—Following a procedure similar to that described in the account of the first operation, a partial extirpation of the right occipital lobe was carried out. The block of excised tissue included the entire lateral surface and posterior portion of the lobe, but none of the medial surface overlying the cerebellum. The calcarine fissure was thus left largely intact except for the posterior three or four millimetres. Subsequent examination of the animal's brain showed that the area striata was intact along the anterior three-fourths of the longitudinal extent of the calcarine fissure. Both the area striata and the visual radiation were either absent or damaged in the posterior one-fourth. Fig. 2 shows the site of the

excision. A more precise statement of the locus and extent of this injury as observed at autopsy is given by Poliak and Rei Hayashi [14].

Post-operative notes.—Same day: There was little activity throughout the day and no sign of visual perception.

First day: There was no evidence of any visual perception, response to moving objects or menacing gestures being absent. The pupils reacted quite promptly to light, however, and apparently equally well to stimulation from all parts of the visual fields. The eyes were sharply deviated to the right.

Second day: There was no response to a well-illuminated banana in any part of the field of vision. Pupillary reactions appeared less brisk

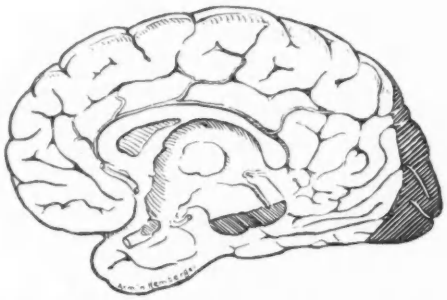

FIG. 2.—Sagittal view of the brain showing the position and extent of the lesion as seen at the second operation.

from the left homonymous side than from the right. Conjugate deviation of the eyes to the right was less pronounced.

Third day: The animal moved around in her quarters more freely, but her actions were like those of a blind person. There was no visual response other than the pupillary reflex.

Fifth day: Flashing an ophthalmoscope into various parts of the visual field gave one the impression that the subject possibly had some awareness of light in the peripheral part of the left homonymous field. There was a complete lack of response to the flashing of the light in the right homonymous field. When allowed to go into the cage outside of the living room for the first time the animal went groping about the cage, bumping into various objects such as posts and suspended automobile tyres. There was nothing in the behaviour of the animal to suggest any useful vision whatever

Eighth day: When examined in the brilliant daylight of the outside cage the animal showed unequivocal response to objects moved and held in the left homonymous visual field. After having eaten several pieces of banana she would reach with surprising accuracy for a piece of banana moved in the left field at distances as great as two feet from the eyes. There was no comparable response when the banana was moved about in the right field. In moving about the cage the animal still seemed to feel its way about rather than to depend upon optical impressions. There was no blinking response to threatening gesture made towards the eyes.

Eleventh day: Occasionally, during the last two or three days, S. seemed to follow pieces of food moving in her left visual field. To-day a more adequate test was made in which the food was moved across the right and left visual fields in random order. Five trials were given on each side. S. responded by reaching for the food each time it was presented in the left visual field and not once in the right field. During the test no word was spoken or noise made that might have provided it with a cue. The blinking response continued to be absent.

Fourteenth day: The blinking response to gestures made towards the eyes was observed for the first time.

Fifteenth day: The animal blinked and cowered when a pretence of striking her was made at a distance of five feet. There was no possibility of responding on the basis of auditory stimuli to these threats as there were steady masking noises.

Sixty-eighth day: Observations by Dr. D. G. Marquis at intervals throughout the period since operation show a progressive increase in visual ability. The animal now responds promptly to food held before it, reaching out with either arm and grasping it accurately. The blinking response to menacing gestures is very definite in the left field, but entirely absent in the right. Objects moved slowly back and forth in front of the eyes are followed with jerky movements, but not with smooth pursuit movements. The animal is now able to move about the cage in apparent normal fashion, climbing on the window ledge and swinging from the roof. It never strikes or bumps into objects even on its blind field.

Seventy-third day: Examination by Dr. M. A. Kennard showed no vision in the right field, and furthermore that this blind region extended somewhat to the left of the mid-line. Left peripheral vision was described as surprisingly keen and accurate.

Acuity Measurements.

The rough threshold determination employing the psychophysical method of limits, in which the size of the stimulus lines is reduced on each succeeding trial until the animal fails, was made three days before the first operation to insure the intactness of the discrimination habit. The value of 0·84 minutes for the test objects at a brightness of 3·98 millilamberts and at a distance of 75 cm. was almost identical with that of 0·85 minutes obtained in the previous extended series of observations [15].

On the sixth day after the *first operation*, S. was given five trials with stimulus lines that were well above threshold. S. responded readily and accurately on each occasion, looking from one stimulus to the other before making her choice. It was observed that the head was invariably turned to the right when looking at the test objects immediately in front of her. There seemed to be little, if any, disturbance of the discrimination habit.

On the ninth day a rough determination of the visual acuity employing the method of limits was made. The value obtained was 0·995 minutes as compared to 0·84 minutes obtained by the same procedure in the retention test given just prior to operation. After this experimental period S. failed to work satisfactorily for almost three weeks, usually responding only two or three times on each occasion. Apparently food motivation was low since S. often opened the food box, took the food and, after examining it, dropped it on the floor. During this time S. was nervous and irritable, and it is possibly of some significance that the genital swelling increased throughout this period and reached the maximum on June 20, the day before S. again worked systematically.

From June 22 to July 6 S. worked excellently and her behaviour compared favourably with that of the pre-operative work. One difference that did stand out, however, was that S. no longer became angry or flew into temper tantrums upon a series of successive failures as had occurred in the pre-operative tests. This difference was apparently not related to lessened motivation as S. worked eagerly for the lure, large cherries, of which she was especially fond.

Visual acuity measurements were made at a distance of 75 cm. in the regular manner at four brightness values of the test-objects, 14·06, 3·98, 0·986, and 0·0176 millilamberts. In Tables 1A and 1B pre-operative and post-operative data are presented showing the percentage of correct responses and the total number of trials given at each size of the

stimulus lines for these several brightnesses. It is apparent that the ranges of the critical stimulus values of the post-operative period, i.e. the points at which the animal responded with an accuracy less than 100 per cent., overlap those of the pre-operative period. At each brightness, however, the accuracy of response decreased more quickly in the post-operative tests than in the pre-operative. The threshold values, taken as the size of the stimulus line at which the animal responded correctly 75 per cent. of the trials, are given in Table II. Inspection shows that the thresholds were slightly, but nevertheless consistently, higher (poorer) at all brightness, in the post-operative tests, visual acuity being between 85 and 95 per cent. of pre-operative vision.

Whether this slight loss represents a genuine loss in visual capacity or whether it is due to other factors is not clear. The behaviour of the animal in the experimental situation after the operation gave no indication that the slightly poorer performance resulted from lessened motivation or attentiveness. Once S. started responding systematically, she worked as willingly and carefully as she had pre-operatively. The one change in behaviour, the absence of rage and temper tantrums after repeated failures, was, if anything, more favourable to careful work since such emotional outbursts were often followed by a series of careless, random responses. This qualitative evidence is further supported by the fact that the average time of response was about the same for both periods, the time increasing to about the same point as the threshold (75 per cent. accuracy) was approached, and decreasing slightly thereafter as more and more random responses were made with the inability to discriminate.

The available evidence suggests, then, that the poorer measures do indicate a genuine but slight loss in efficiency of the visual system. This conclusion is further strengthened by the fact that at 3·98 millilamberts three independent measures of visual acuity, obtained by different psychophysical procedures [15], gave highly consistent measures of 0·81, 0·84 and 0·85 minutes while two post-operative measures gave 0·98 minutes and 0·995 minutes. The loss is slight, however, and by no means proportional to the amount of the visual system that was destroyed.

No attempt was made to test S.'s visual acuity until the sixteenth day after the *second operation* as there was little evidence before this of visual function other than that of light or movement perception. She refused to work on this occasion and took food only when it

was given through the small opening of the apparatus. Even with the room lights on she groped around in blind fashion.

S. remained unco-operative for several days, even refusing to go into the experimental cage. On the twenty-first day, however, she worked for twenty trials. The test fields were at a brightness of 3·98 millilamberts and the stimulus lines in the positive field were fairly

TABLE Ia.—SHOWING THE PERCENTAGE OF CORRECT RESPONSES AND THE TOTAL NUMBER OF TRIALS GIVEN AT EACH SIZE OF THE STIMULUS LINES.

Visual angle in minutes	Brightness of test objects (millilamberts)							
	0·176				·986			
	Pre-operative		Post-operative		Pre-operative		Post-operative	
	Per cent. correct	Number of trials	Per cent. correct	Number of trials	Per cent. correct	Number of trials	Per cent. correct	Number of trials
2·141			100·0	20				
1·985	100·0	40	95·0	20				
1·871	90·0	80	90 0	20				
1·737	86·3	80	80·0	15				
1·636	88·8	80	80 0	15				
1·542	75·0	80	53·0	15				
1·464	70·0	70						
1·392	62·5	40						
1·325	53·3	30						
1·265							100·0	15
1·211							95·0	20
1·160							80·0	20
1·114					100·0	30	75·0	20
1·070					96·7	30	80·0	20
1·030					91·7	60	60·0	25
0·995					91·7	60		
0·961					83·3	60		
0·929					81·0	60		
0 899					67·5	80		
0·871					63·3	60		
0·845					50·0	20		

large, subtending a visual angle of 13·8 minutes at a distance of 75 cm. In twenty trials the animal responded correctly only nine times, indicating that she was quite unable to discriminate lines of this size. Her behaviour, however, suggested that she could at least differentiate between the two circular stimulus fields, for in the early trials she appeared to look back and forth from one test field to the other before making a choice. In the latter part of the period she became restless and usually responded immediately after the sliding door was raised

without looking in the direction of either stimulus object. However, in neither half of the period did S. make a significantly greater number of correct responses than might be expected by chance, i.e. one-half.

TABLE Ib.—SHOWING THE CORRECT RESPONSES AND THE TOTAL NUMBER OF TRIALS GIVEN AT EACH SIZE OF THE STIMULUS LINES.

Visual angle in minutes	Brightness of test objects (millilamberts)							
	3·98				14·06			
	Pre-operative		Post-operative		Pre-operative		Post-operative	
	Per cent. correct	Number of trials	Per cent. correct	Number of trials	Per cent. correct	Number of trials	Per cent. correct	Number of trials
1·160			100·0	20				
1·114			95·0	20				
1·070			84·0	25				
1·030	100·0	20	80·0	25				
·995	100·0	20	84·0	25	100·0	20		
·961	93·3	60	60 0	25	100·0	30		
·929	93·0	70	59·0	10	96·7	60	100.0	10
·899	81·4	70			93·3	60	90·0	10
·871	81·4	70			91·6	60	80·0	10
·845	75·0	60			90·0	60	50·0	10
·820	70·0	60			80·0	60		
·797	62·0	50			86·7	60		
·775	55·0	20			73·3	60		
·754					71·0	80		
·735					56·7	60		
·716					50·0	10		

TABLE II.—SHOWING THRESHOLDS (VISUAL ANGLE IN MINUTES) FOR THE PRE-OPERATIVE AND POST-OPERATIVE PERIODS.

Experimental period	Brightness of test objects (millilamberts)			
	14·06	3·98	·986	·0176
Pre-operative	·78	·85	·92	1·54
Post-operative	·87	·98	1·07	1·62
Pre-operative / Post-operative	·896	·867	·86	·95

VISUAL FIELD DETERMINATIONS.

Determination of visual field defects in animals is a most difficult matter. Attempts were made, however, to discover the effects of the operations upon the limits of the visual fields by the method of

presenting to the animal in a more or less systematic fashion moving pieces of food or other objects in various portions of its visual fields and observing the responses of the eyes and the attempts of the animal to obtain the food. The crudity of these methods requires, of course, that the observations be accepted and interpreted with considerable caution.

The results of these studies suggest that after unilateral destruction of the left striate area there was a right homonymous hemianopsia. That this loss in the right fields was complete, including at least a part of a macular vision, is suggested by the post-operative note of the third day to the effect that the eyes fixated only when the object had reached the mid-line. This conclusion receives added support from the observation that the animal always turned its head well to the right when looking at the test objects.

The second operation further delimited the fields of vision so that only the extreme left peripheral regions, probably corresponding to the temporal half-moon [9], remained functional. That there was in all probability a central scotoma is suggested by the following observations: (1) When objects were moved from the right field to the left no response was made until the object reached a point some distance to the left of the mid-line; (2) the animal never picked up objects directly in front of it but always turned its head to the side. The very low visual acuity test results, i.e. failure to discriminate a pattern of lines subtending an angle as large as 13·8 minutes, also support this conclusion.

Discussion and Interpretation of Results.

The relation of visual acuity to the neurological elements, both peripheral and central, is a complex one, about which comparatively little is known. However, the studies of Hecht and others [3, 4, 5, 6] have presented fairly clear-cut evidence suggesting that visual acuity is a function of the density or grain of the elements, rods and cones, in the retina. The most important fact in support of this conclusion is that visual acuity varies in different parts of the retina according to the density of the elements, being greatest in the macular area where there are the greatest number of elements per unit area and least in the peripheral regions in which the independent elements are less dense.

It will readily be seen, then, that the effect on visual acuity to be expected from the removal or destruction of any part of the visual cortical elements will depend upon the nature of the relation of these structures to those of the retina. The effects on the fields of vision resulting from partial and complete unilateral occipital lobectomies

have led to one conception of this relationship as involving a strict anatomical point-to-point projection of the retina upon the visual cortex. This view very successfully accounts for the cases of small circumscribed scotoma resulting from limited lesions and for the various quadrantic and hemianoptic defects resulting from larger partial and complete unilateral lesions.

Objections have been raised, however, to this conception of a specific, fixed relationship, particularly in the case of macular vision. The critics, while willing to recognize some degree of specific localization, deny that this organization is anything more than a crude one. The strict localistic principle does not hold, they claim, for the finer internal organization of the macular area. These objections are based upon various observations, one of the most important of which is the preservation of central vision (macular sparing) that sometimes occurs in cases of supposed, complete unilateral damage to the visual cortex. Such cases, if really involving a complete unilateral ablation, are truly embarrassing for this point of view. They are, on the other hand, nicely explained on the basis of a diffuse organization of the macula such that the fibres from the various parts of each macula are distributed in a random manner to both visual cortical areas. The ablation of one of these areas would result in no particular portion or area of the maculæ becoming functionless but only in a reduction in the density or number of the elements throughout each total macula.

The implication of this latter view for visual acuity measurements is obvious. With the reduction in the density of the functional elements, which would presumably be decreased about half, as this proportion of the macular fibres are estimated to cross in the chiasma, a corresponding loss in visual acuity would be expected. This expectation was not realized in the present investigation. Further evidence contradicting such a view is the fact that there is no macular sparing in cases in which the optic tract itself is completely interrupted, thus showing that fibres from the temporal halves of the maculæ do not cross over to the opposite hemisphere, at least not by way of the optic chiasma.

A somewhat different hypothesis that has been put forward to explain these cases of macular sparing is that a portion of the visual radiation crosses to the striate area of the opposite hemisphere through the splenium of the corpus callosum [1, 2, 7, 10, 11, 12, 16]. The results of the present experiment are not conclusive as regards this hypothesis, as the effect on visual acuity of a unilateral occipital lobectomy to be expected on the basis of it would depend on several things. First of all,

it would be a function of the proportion of the macular fibres that cross in the corpus callosum, and it also would depend upon whether the decussating fibres provide dual cortical representation, i.e. by a branching of the individual fibres from the macular elements, one branch decussating to the opposite hemisphere and the other continuing to the ipsilateral one, or whether there was simply a single cortical element corresponding to each macular element.

If we assume that the proportion of decussating fibres is about half and that it is roughly an alternate fibre affair, the effect of complete destruction of the left occipital cortex would be as follows: (1) With the further assumption that the decussating fibres provide dual cortical representation, the density of the grain in the ipsilateral homonymous hemi-maculæ would be decreased by half with an approximately corresponding decrease in visual acuity. However, the density of the elements in the contralateral or right halves of each maculæ would not be decreased and consequently visual acuity measurements would not be expected to show any decrease unless confined to the left hemimaculæ. (2) On the assumption that the crossed fibres do not provide double cortical representation, i.e. that there is no branching of the macular fibres, the density of the grain in both halves of each maculæ would be decreased by half and one would thus expect a corresponding decrease in visual acuity. The results of the present experiment are not in harmony with the latter variation of the hypothesis. To determine the validity of the former, determination of visual acuity for different regions of the maculæ is needed. Such a study would require the co-operation that only human subjects can provide.

The purpose of the second operation was to determine whether the macula of the chimpanzee, as Poliak has demonstrated for the monkey [13], is projected on the posterior portion of the striate area in the region of the occipital pole. In this operation the posterior one-fourth, including the entire lateral surface of the right occipital lobe, was either damaged or removed. There was thus a complete bilateral removal of the supposed macular cortical areas. In such a subject central vision should be non-existent.

The experimental tests of visual acuity and observations of field defects tended to confirm this expectation. Visual acuity was considerably below that to be expected of the macular region for even the lowest illuminations, while the visual field tests indicated that vision was present only in the extreme peripheral portion of the left field. This latter observation is also in agreement with the numerous studies of men, which

show that the far periphery of the visual field [9], the temporal half-moon or crescent as it is sometimes termed, is projected on the anterior part of the area striata along the calcarine fissure, the only portion of the lobe left intact by the operation.

Summary and Conclusions.

This investigation is concerned with the relation of the visual cortical areas to visual acuity. An adolescent chimpanzee whose visual acuity had been carefully determined by the Ives visual acuity test object over an intermediate range of brightness levels was subjected to the following operations: (1) Complete extirpation of the left occipital lobe; and (2) extirpation of the posterior and lateral portions of the area striata of the right hemisphere.

Subsequent to each operation visual acuity measurements were made with the following results :—

(1) The removal of the entire left area striata resulted in a slight, but consistent loss in visual acuity ranging from approximately 5 to 15 per cent. at four brightness levels.

(2) Following the second operation, which left the animal with only the anterior portion of the right area striata intact, there was complete failure to discriminate a pattern sixteen times as large as that discriminated in the pre-operative tests.

Rough testing of the visual fields suggested that a right homonymous hemianopia resulted from the first operation, while the second spared only the extreme left peripheral fields, i.e. the temporal half-moon. This latter result supports the view that the occipital pole of the area striata represents the macular projection area and the anterior portion of the area striata around the calcarine fissure is the cortical terminus of the extreme peripheral retinal elements.

References.

[1] Foerster, O. "Beiträge zur Pathophysiologie der Sehbahn und der Sehsphäre," *Journ. f. Psychol. u. Neurol.*, 1929, **39**, 463-485.

[2] Foerster, O., and Penfield, W. "Der Narbenzug am und im Gehirn bei traumatischer Epilepsie in seiner Bedeutung fur das Zustandekommen der Anfalle und fur die therapeutische Bekampfung derselben," *Zeitschr. f. d. ges. Neurol u. Psychiat.*, 1930, **125**, 475-572.

[3] Hecht, S. "The Relation between Visual Acuity and Illumination," *Journ. Gen. Physiol.*, 1928, **11**, 255-282.

[4] *Idem.* "The Nature of the Photoreceptor Process. Foundations of Experimental Psychology." Worcester, Mass.: Clark Univ. Press, 1929, pp. x + 907.

[5] Hecht, S., and Wald, G. "The Influence of Intensity on the Visual Functions of Drosophila," *Proc. Nat. Acad. Sciences*, 1933, **19**, 964-972.

[6] HECHT, S., and WOLF, E. "The Visual Acuity of the Honey Bee," *Journ. Gen. Phys.*, 1929, **12**, 727-760.

[7] HENSCHEN, S. E. "Sur les localisations dans le ganglion genicule extreme," *Rev. Neurol.*, 1897, **5**, 619-620.

[8] IVES, H. E. "A Visual Acuity Test Object," *Electrical World*, 1910, **55**, 939-940.

[9] KRONFIELD, P. C. "The Temporal Half-moon," *Trans. Amer. Ophthal. Soc.*, 1932.

[10] LENZ, G. "Zur Pathologie der zentralen Sehbahn unter besonderer Berucksichtigung iherer Ergebnisse fur die Anatomie und Physiologie," *Arch. f. Ophthal.*, 1909, **72**, 1 and 187.

[11] PENFIELD, W., and EVANS, J. "Functional Defects Produced by Cerebral Lobectomies," *Proc. Assoc. Research Nerv. and Ment. Dis.*, 1932, **13**, 352-378.

[12] PENFIELD, W., EVANS, J., and MACMILLAN, J. A. "Visual Pathways in Man, with Particular Reference to Macular Representation," *Arch. Neur. and Psychiat.*, 1935, **33**, 816-834.

[13] POLIAK, S. "The Main Afferent Fiber Systems of the Cerebral Cortex in Primates." Berkeley, Cal.: Univ. Cal. Press, 1932, **2**, xiv + 370.

[14] POLIAK, S., and HAYASHI, REI. "The Cerebral Representation of the Retina in the Chimpanzee," *Brain*, this issue.

[15] SPENCE, K. W. "Visual Acuity and Its Relation to Brightness in Chimpanzee and Man, *Journ. Comp. Psychol.*, 1934, **18**, 333-361.

[16] WILBRAND, H., and SAENGER, A. "Handbuch der Neurologie des Auges." Weisbaden: J. F. Bergmann, 1917, **7**.

[17] YERKES, R. M., and WATSON, J. B. "Methods of Studying Vision in Animals," *Behav. Monog.*, 1911, **1**, No. 2.

THE CEREBRAL REPRESENTATION OF THE RETINA IN THE CHIMPANZEE.[1]

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THE great strides made during the past twenty years in revealing the internal organization of the afferent visual pathway in man and other primates are chiefly due to careful experimental and pathologico-anatomical investigations. It has been said that the anatomical study of the brain in cases of disturbance of the visual fields has lagged behind the clinical analysis, but this defect has been remedied in recent years by the work of Holmes [4, 5], Brouwer [1, 2], Pfeifer [8], and others, in which the central portions of the visual pathway, the optic radiations and the striate area (field 17) have been examined.

This work, together with the investigations of Rönne [14], of Brouwer and Zeeman [3], of Juba [6], and of Le Gros Clark and Penman [7] on the composition of the peripheral parts of the visual pathway from the retina to the lateral geniculate bodies, and with the studies of the central portion of the visual pathway from the lateral geniculate bodies to the striate area of the cerebral cortex undertaken by one of the present writers [Poljak, 9, 10, 11, 12, 13], and by other investigators in recent years, have helped to provide a fairly detailed conception of the internal structure of the entire afferent visual system; that is, of the position of the different quadrants and in particular of the macula in the optic nerve and tract, in the lateral geniculate body and in the striate area.

The result of all these investigations may be briefly stated as follows: The optic nerve-fibres originating in the retinal periphery corresponding with the upper and lower quadrants of the retina terminate in the medial and lateral segments of the lateral geniculate bodies respectively. The optic nerve-fibres originating in the macula terminate in the large intermediate segments of the lateral geniculate bodies. The most dorsal and the most ventral bundles of the visual radiation originate

[1] This work was undertaken with the help of grants from the Douglas Smith Foundation and from the Josiah Macey Junior Foundation.

in the medial and lateral segments of the lateral geniculate body respectively, terminate in the upper and lower lip of the calcarine fissure, and correspond with the upper and lower extramacular quadrants of the retinæ respectively. The intermediate bundle of the visual radiation originates in the large intermediate segment of the lateral geniculate body, is placed between the "peripheral" bundles (has an "axial" position in the radiation), is the longest of all and terminates in the posterior portion of the striate area around the tip of the occipital lobe. This bundle and its terminal cortex correspond with the homonymous halves of both maculæ.

As is well known, in the attempts to determine the inner composition of the afferent visual system, experiments on monkeys have played a conspicuous role. For this reason it was considered of some value to report the following case of a chimpanzee operated upon and observed during a period of more than five months by Professor J. Fulton, of Yale University, who kindly sent its brain to one of us. (This animal, under the name of "Kani," female, weighing 35 kg., came from Professor Yerke's division of the Yale University where it was used for the study of visual acuity.)[1]

The following is a brief extract from a protocol of Professor Fulton on the operations performed and on the behaviour of the ape:—

In the first operation a radical extirpation of the entire left occipital lobe, including all of the calcarine cortex, was made. On the next day the eyes deviated to the left, but were capable of extreme deviation to the right also. This tendency to deviate disappeared during the next few days. The right pupil was slightly larger, but this difference disappeared on subsequent days. The palpebral fissures were equal. There was no nystagmus. On the second post-operative day, upon gross examination, there was an obvious and apparently complete right homonymous hemianopsia which seemed to disturb the visual behaviour of the animal very little. On the third day no vision in the right homonymous halves could be detected, the deficit reaching exactly to the vertical meridians. This complete right-sided hemianopic blindness remained without change until the death of the animal five months and five days later (reckoned from the date of the first operation).

Forty-four days after the first *the second operation* was undertaken: *sub-total removal of the right occipital lobe.* The purpose of the second experiment was *to remove the region of the occipital lobe which in man and monkey contains the macular representation*, viz. the lateral surface of the occipital lobe, leaving intact the portion of the calcarine fissure coursing along the medial surface of

[1] The results of the physiological examination of the same case are being published in a separate paper in this journal by Prof. Fulton and Dr. Spence. After having read the manuscript we are glad to acknowledge our satisfaction with the high degree of accuracy of their work.

the hemisphere. On the first post-operative day, when the animal was at rest, there was a tendency toward the deviation of the eyes to the right with a very marked nystagmus with slow component to the right, and occasional vertical nystagmus. The various tests applied revealed no sign of visual perception of moving objects, or of strong light. No blink-reflex or response to any sort of visual stimuli was noticeable, and whenever touched the animal was evidently surprised, as would be a normal animal in darkness. On the fifth day, flashing an ophthalmoscope into various parts of the visual fields gave the impression of a possible awareness of light in the peripheral parts of the left homonymous fields, although this was not yet certain. On the eighth day the animal showed an unequivocal response to objects moved and held in the left homonymous visual fields. After she had eaten one or two pieces of banana she reached for a banana held or moved in the left fields at distances as great as two feet. There was no comparative response in the right homonymous fields. Her accuracy in localizing the objects was surprising, often coming within inches and striking the observer's wrist, for example. There was no blinking response to threatening gestures made toward the eyes. In moving about the cage she seemed to feel her way rather than to depend upon visual impressions, but when excited she chased the observer and seemed to be able to localize him when there were no obvious auditory cues. Fourteen days after the second operation, for the first time, it was possible to observe the winking response to gestures made toward the eyes. There was an unmistakable response to movements in the left homonymous visual fields, but not to movements in the right fields. No difference between the superior and inferior fields (quadrants) could be detected. This situation remained the same in all particulars during almost five months after the second operation. Even on the day that the animal was sacrificed it still responded only to visual stimuli falling in the periphery of the left homonymous fields, without evidence of a useful central (foveal, macular) vision. Otherwise, during the observation, no pathological signs other than the visual defects were noticed.

The histological examination of the serial sections stained with thionine blue, made by the authors, revealed the following pathological changes :—

In *the left cerebral hemisphere* there was a complete absence of the striate area of Elliot Smith, i.e., the field 17 of Brodmann. As a consequence of this it was found that the nerve-cells of the left lateral geniculate body were completely degenerated, no trace of normal cells being left in any part of the nucleus. There was also marked partial degeneration in the pulvinar of the left thalamus due to the partial injury of the area peri-para-striata or fields 18-19. The left corpus or griseum prægeniculatum was found to be normal. Because of the above findings the left hemisphere will not be further considered in the following.

The *right cerebral hemisphere* showed a more restricted lesion limited chiefly to the tip or pole of the occipital lobe (stippled areas in fig. 1. The narrow crudely shaded area indicates the normal striate area hidden in the calcarine fissure). The cross-sections through the right occipital lobe (fig. 2) revealed a complete absence of that portion of the striate area which in the chimpanzee normally spreads over the occipital pole to its lateral surface along the external calcarine sulcus (the exact limits of the lesion in the drawing A, in fig. 2, are not given, but merely the outlines of the actual section; the approximate extent

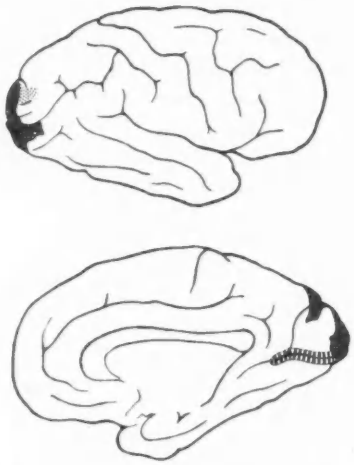

FIG. 1.—Right cerebral hemisphere of a chimpanzee showing in the upper figure a lateral view, in the lower figure a medial view. Damaged portion of the occipital lobe still present is indicated by stippling, the longitudinal extent of the normal striate cortex is indicated by coarse shading. The striate area in reality does not appear on the surface of the brain but is hidden in the calcarine fissure. (Compare crudely shaded portions of the cortex in fig. 2.)

of the removed substance can easily be noted). A limb of the lesion (stippled) penetrates into the substance of the lobe from below and interrupts a considerable portion of the lower or ventral bundles of the visual radiation (vr). A similar destruction of a portion of the cortex coating the upper lip of the calcarine fissure (fc) can be considered as its counterpart. (In the drawing A this portion of the destroyed cortex is missing, in the drawing B a small triangular lesion partly undermines the cortex in the upper lip.) The last vestiges of the two mentioned lesions—the one in the upper portion of the visual radiation, and the other in the lower portion of the radiation—are still visible in

the drawing C, in fig. 2, but anteriorly, in the drawing D of the same figure, only the normal cortex and the normal visual radiation were present. Possibly, the vertical or macular branch of the radiation was somewhat atrophic; this, however, was difficult to evaluate owing to the method of staining applied (thionine-blue). The approximate extent of the normal striate cortex as seen when projected upon the inner face of the hemisphere is represented by a narrow, vertically-shaded area in the lower drawing in fig. 1, stretching along the

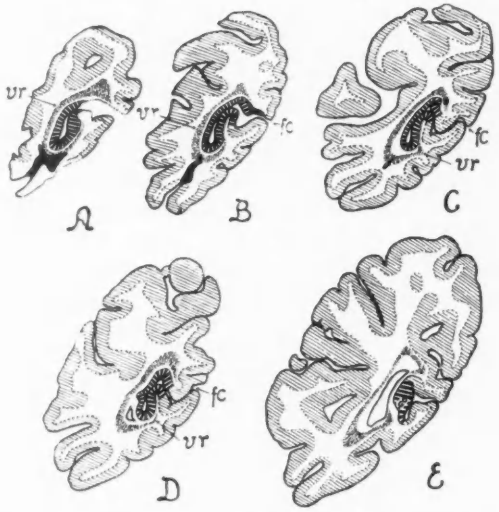

FIG. 2.—Transverse sections through the right occipital lobe depicted in fig. 1. The caudal end of the lobe in the drawing A. The normal portions of the striate cortex crudely shaded, the non-striate cortex lightly shaded, the lesion stippled; fc = calcarine fissure; vr = visual radiation.

calcarine fissure. In order to evaluate the extent of the damage to the visual pathway and to the visual projection cortex it is necessary to consider that the cortex in the depth of the calcarine fissure along its greater anterior and middle longitudinal extent does not receive its afferent visual or any other fibres directly, that is, from the segment of the visual radiation apparently nearest to it (which would be the vertical branch of the radiation, thus in the drawings B, C, D, in fig. 2), since this vertical portion of the radiation is separated from the calcarine cortex by the lateral ventricle (visible only in the drawings D and E, in fig. 2), or by its vestige, thus forcing the incoming or outgoing fibres to

turn around the ventricle either from below or from above in order to reach or to leave the "calcar avis." (Exceptions are the "axial" or macular bundles that pass straight to the tip of the occipital pole, the same that in the aggregate form the vertical branch of the radiation.) Since in our case there was some damage done to just the two-mentioned localities, as illustrated by the two small lesions in the upper and in the lower segments of the visual radiation (in the drawings B and C, in fig. 2)

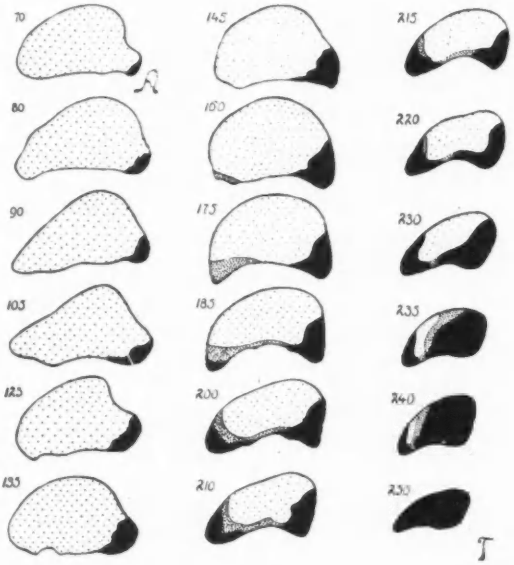

FIG. 3.—Serial sections at fairly regular intervals through the entire lateral geniculate body of the right side, ipsilateral with the lesion. The caudal end of the nucleus is at the drawing A, its rostral beginning at the drawing T. The left sides of the individual drawings are the inner or medial, the right sides of the drawings are the outer or lateral. The normal portions of the nucleus are in solid black, the completely degenerated are lightly stippled, the atrophic ones are densely stippled.

the amount of the striate cortex deprived of afferent fibres is somewhat larger than the striate cortex actually destroyed. It is also to be considered that the subcortical, direct damage to the lower segment of the radiation in the lower lip of the calcarine is somewhat more extensive than that to the upper segment in the upper lip of the calcarine fissure. In any event it can be said that in our case the anterior portion of the striate area and its afferent fibres of the visual radiation remained wholely intact.

The extent of the complete retrograde degeneration (fig. 3, thinly stippled areas) or of the atrophy of the nerve-cells (densely stippled areas) in *the right lateral geniculate body*—the consequence of the cortical injury to the afferent nerve-fibres taking origin from the nerve-cells of the mentioned nucleus—is illustrated in fig. 3 (normal portions black; the accompanying numbers indicate the sections). The first that one notices is that in the sections closer to the caudal end of the lateral geniculate body (this end is at A) the degeneration is more complete, extending almost over the entire nucleus, not sparing even the large cells of the ventral layers. Only the tip of its lateral segment preserved a nest of approximately normal large nerve-cells. As one proceeds toward the middle of the longitudinal extent of the nucleus (middle column in fig. 3), the degeneration, while still occupying the bulk of the nucleus, becomes gradually narrowed by the increasing medial and lateral zones where the cells appear normal or only more or less atrophic. These normal zones occupy chiefly the two outward segments, the innermost or the medial, and the outermost of the lateral (left and right, respectively, in the individual drawings, in fig. 3), both zones or segments being barely connected with one another by means of a narrow zone spreading along the lower or ventral contour of the nucleus. In sections corresponding with the anterior or rostral one-third of the geniculate body (right column in fig. 3) this more or less normally appearing strip increases somewhat in thickness, although even in the most anterior sections of the nucleus (close to T in the right column, fig. 3) a narrow strip that touches the ventral contour remains where the nerve-cells do not appear quite normal. On the other hand, in the oral one-third of the nucleus the relative sizes of the normal segments increases until near its anterior end almost the entire nucleus appears to contain normal nerve-cells.

In trying to correlate the size and location of the lesion in the right occipital lobe with the size and location of the retrograde cell-degeneration of the lateral geniculate body of the right side we are at some disadvantage because the exact projection of the various peripheral and macular quadrants of the retina upon the lateral geniculate body in the chimpanzee is not known. Yet we think that a certain comparison with the geniculate projection in man and in lower monkeys known from the investigations of Rönne, Juba, Brouwer-Zeeman and Le Gros Clark-Penman is permissible, at least as an approximation. From this we conclude that in the champanzee, too, the macular portions of both retinæ are projected upon the large intermediate segment placed more

toward the caudal end of the lateral geniculate, while the upper and lower extramacular quadrants are represented in the medial and lateral segment, of the same nucleus respectively. If this be correct—as it is very likely—then the portion of the lateral geniculate nucleus degenerated in our case corresponds chiefly with the hemimaculæ, the portions remaining normal correspond with the extramacular portions of the homonymous hemiretinæ including the monocular crescent. This in turn leads to the conclusion that the anterior portion of the striate area which lines the posterior and larger portion of the calcarine fissure—which in our ape remained largely intact (crudely shaded narrow area in fig. 1)—corresponds also with the extramacular portions of the retinæ, or of the visual fields respectively, whereas the portion of the striate area covering the tip of the occipital lobe and spreading over its postero-lateral face, removed in our case, is the portion where the hemimaculæ, respectively the centres of the visual fields, are represented.

This all fits very well with the character of the observed defect of the fields of vision, where the central portions were absent on the left side during the life of the animal, which extended over almost five months after the second operation. This, too, is in perfect accord with those numerous observations of the human cases which have led to the conviction that the macular representation is near the tip of the occipital lobe, in the caudal portion of the striate area. True, the absence of an exact perimetric study of the functional loss in our case, and the fact that the extent of the macular territory in the lateral geniculate body is not known in the apes and was here merely conjectured from the analogy with the human conditions [Rönne, Juba] permits only an approximation. Nevertheless, our case shows that the assumption made earlier and again in recent times, viz., that the macula may partly be represented in the anterior portion of the striate area, or that the macula is diffusely represented, is ill-founded. The large size of the degenerated segment of the lateral geniculate body, ample enough for the entire macula, even if its size is generously measured, tells against the above assumption. (In fact, we suspect that considerably more than the macular cortex proper was eliminated in our experiment.) At least it appears that the anterior portion of the striate area, which in our case remained intact, is in no way directly connected with central or macular vision. On the other hand, for the problem of quadrantic representation there is little of value in the present case. Perhaps the smaller size of the inner or medial segment of the lateral geniculate body that remained normal (left ends of the

drawings in fig. 3) in comparison with the lateral segments (right ends of the drawings in fig. 3) is due to the larger lesion that interrupts the upper portion of the visual radiation and the upper lip of the calcarine fissure (thus in the drawings A, B in fig. 2) if compared with the smaller lesion damaging the lower lip of the calcarine fissure (small stippled areas in B and C, in fig. 2). This, too, would conform to the generally accepted schema according to which the upper quadrants of the retinæ (lower quadrants of the visual fields) are represented in the upper lip of the calcarine fissure and in the upper or dorsal bundles of the visual radiation; the lower quadrants of the retinæ (upper quadrants of the visual fields), on the contrary, in the lower lip of the calcarine fissure and in the lower bundles of the radiation.

Finally, the completeness of the degeneration of the nerve-cells in the intermediate segment of the lateral geniculate nucleus does away with the assumption that any number of the nerve-cells composing the lateral geniculate nucleus may be the so-called intercalated or associational elements, cells with a short axis cylinder of the Golgi type II. The same fact is also inconsistent with the view that some of the geniculate cells, especially the large ones, may send their axis cylinders to the superior colliculi or elsewhere and not to the cortex. It is more plausible that, since all geniculate cells—including the large ones in the ventral layers of the nucleus—completely disappear in consequence of the lesion to the occipital lobe, all of them give rise to axis cylinders which terminate in the striate area.

The fact that the circumscribed lesion of the caudal end of the striate area produces a sharply delimited degeneration in the intermediate or macular segment of the lateral geniculate body once more disproves Monakow's concept still adhered to by some, viz., that the macular fibres of the visual radiation spread over the entire territory of the striate area. Our case shows that the macular fibres have a well delimited area in the cerebral cortex, the posterior portion of the striate area, beyond which they do not reach. This concept is based chiefly upon numerous observations of central scotomata of restricted size, and it is also in full agreement with the results of the experiments upon the macular cortex (P. '33) and of the study of the minute structure of the retina in Primates (P. '35), both of which show that it is just the macula and the macular portion of the entire afferent visual system where the "projection" of the retina is most elaborate, where the size of its composing elemental structural-functional units is the smallest, where their number is the greatest, and where their

separation from one another is farthest advanced or is most complete. In conclusion, let us call attention to the surprisingly large degree of visual function which was preserved in our ape although only a fraction of its total nervous-visual mechanism was left intact.

REFERENCES.

[1] BROUWER, B. "Ueber die Projection der Makula auf die Area striata des Menschen," *Journ. f. Psychol. u. Neurol.*, 1930, **40**, 147.

[2] *Idem.* "The Projection of the Retina on the Cerebral Cortex in Man." In "Localization of Function in the Cerebral Cortex," published by Assoc. for Res. in Nerv. and Ment. Dis., 1932, **13**, 529.

[3] BROUWER, B., and ZEEMAN, W. P. C. "The Projection of the Retina in the Primary Optic Neuron in Monkeys," *Brain*, 1926, **49**, 1.

[4] HOLMES, G. "A Contribution to the Cortical Representation of Vision," *ibid.*, 1931, **54**, 470.

[5] *Idim.* "The Representation of the Mesial Sectors of the Retinæ in the Calcarine Cortex." *Jahrb. f. Psychiat. u. Neurol.*, 1934, **51**, 39.

[6] JUBA, A. "Ueber das Projektionsfeld des zentralen Sehens im äusseren Kniehöcker und in der Sehrinde des Menschen," *Zeitschr. f. d. g. Neurol. u. Psychiat.* 1933. **147**, 121.

[7] LE GROS CLARK, W. E., and PENMAN, G. G. "The Projection of the Retina in the Lateral Geniculate Body," *Proc. Roy. Soc.*, London, Ser. B., 1934, **114**, 291.

[8] PFEIFER, R. A. "Hirnpathologischer Befund in einem Fall von doppelseitiger Hemianopsie mit Maculaaussparung," *Journ. f. Psychol. u. Neurol.*, 1930, **40**, 319.

[9] POLJAK, S. "The Main Afferent Fiber Systems of the Cerebral Cortex in Primates," University of California Press, Berkeley, California, 1932.

[10] *Idem.* "Projection of the Retina upon the Cerebral Cortex, based upon Experiments with Monkeys." In "Localization of Function in the Cerebral Cortex," published by Assoc. for Res. in Nerv. and Ment. Dis., 1932, **13**, 535.

[11] *Idem.* "A Contribution to the Cerebral Representation of the Retina," *Journ. Compar. Neurol.*, 1933, **57**, 541.

[12] *Idem.* "Structure of the Retina in Primates." *Acta Ophthalm.*, 1935, **13**, 52.

[13] *Idem.* "Minute Structure of the Retina in Monkeys and Apes," *Arch. Ophthalm.* (in print).

[14] RÖNNE, H. "Die anatomische Projektion der Macula im Corpus geniculatum ext.," *Zeitschr. f. d. g. Neurol. u. Psychiat.* (Orig.), 1914, **22**, 469.

THE PITUITARY-HYPOTHALAMIC MECHANISM: EXPERIMENTAL OCCLUSION OF THE PITUITARY STALK.

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INTRODUCTION.

THIS work is directed towards an elucidation of the rôle played by the hypophyseal stalk in linking the activities of the pituitary body and hypothalamus. The pituitary stalk has previously been regarded as a pathway for the secretion of the pars intermedia to the pars nervosa and base of diencephalon, and secondly as a possible mediator of nerve impulses from the hypothalamus to the pituitary body. It was believed that there existed a reciprocal interaction between certain of the hypothalamic nuclei and the pituitary gland and this has given rise to the conception of a pituitary-hypothalamic mechanism.

In the past experimental diabetes insipidus has been produced both by hypophysectomy (Vassale and Sacchi [31], Crowe, Cushing and Homans [8], and Richter [26]), and by isolated lesions of the hypothalamic nuclei (Aschner [1]), Camus and Roussy [7], Houssay [16], Bailey and Bremer [2], Bourquin [5 and 6]). The evidence has been reviewed extensively by Lhermitte [20], Roussy and Mosinger [27], Leschke [19], Staemmler [28] and Biggart [4], and appears equally in favour of the hypophysial and of the hypothalamic origin. With the gradual acceptance of the neural and vascular connections, an attempt has been made to bring together the two conflicting views. Thus Fisher, Ingram and Ranson [12] have recently brought forward evidence to show that in cats, injury of the tuber cinereum, causing bilateral destruction of the supra-optic-hypophyseal tract, results in atrophy of the supra-optic nuclei, atrophy of the posterior lobe, and a permanent upset in the water balance. They concluded that damage to this neural connection at any of three points, namely the nucleus, the fibre tract or the posterior lobe will produce experimental diabetes insipidus.

The results presented in this communication were obtained by complete obstruction of all pathways both for secretion and for nerve

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impulses between the pituitary body and the hypothalamus. The physiological findings show a striking difference in dogs and monkeys following the same procedure and there is a structural variation in the two species which accounts for this difference. The results show that the view put forward by Fisher, Ingram and Ranson for the cat is not applicable to the monkey and may therefore not be tenable in man.

Previous Work on Occlusion of the Pituitary Stalk.

Physiological studies following experimental division or occlusion of the pituitary stalk are few. Towards the end of his important monograph "L'Hypophyse du Cerveau," Paulesco [23] in 1908 reported briefly the results of experiments on six dogs in which the pituitary stalk had been divided and the gland left intact in the sella turcica. He concluded that such a procedure was equivalent to a total or nearly total hypophysectomy. In one of these animals, which succumbed within twenty hours following operation, the pituitary body was found turgid, hæmorrhagic and the cells in process of degeneration. Two others died within twenty hours of the operation, the remaining three living six, eighteen, and twenty-four days respectively. Except for brief mention of an immediate post-operative sleepy state and the absence of glycosuria in one of the series, no details were given of the post-operative course or post-mortem findings in these animals.

Crowe, Cushing and Homans [8] made an extensive study of experimental hypophysectomy in 1910 and reported five more dogs in which the pituitary stalk was divided. Two of these succumbed with all the symptoms of "cachexia hypophysiopriva," one on the tenth day and one after twenty-four days. Another animal was successfully tided over a period of threatened "cachexia hypophysiopriva" by injections of "anterior lobe extract," and lived five months, gradually increasing in weight but in all other respects apparently normal. The other two animals showed no tendency towards development of cachectic symptoms and were sacrificed on the twelfth and twenty-eighth post-operative days respectively, for histological purposes. In all cases marked degenerative and atrophic changes were found in the pituitary, most marked in the pars distalis, but in three animals which did not succumb to cachectic symptoms and which were ultimately sacrificed, persistent areas of normal-appearing epithelial cells were seen. The pars nervosa was usually more normal in size and was invaded by cells of the pars intermedia. There was an overabundance of hyaline throughout the pars nervosa and many colloid cysts in its epithelial investment. They

interpreted their findings, so far as the pars distalis was concerned, as being due to interference with its major blood supply along the infundibular stalk. "The resultant condition . . . is almost the same as if this portion of the gland had actually been removed and then reimplanted like a graft, for the circulation is almost entirely cut off." In so far as the histological appearances of the pars nervosa were strongly suggestive of a damming back of colloid material, the experimental data of Crowe, Cushing and Homans appeared to fit in with the conception of secretion originating in the pars intermedia and passing through the pars nervosa and infundibular stalk to the base of the third ventricle.

Following these earlier studies on pituitary stalk section, Cushing and Goetsch [9, 10] adopted the method of placing a silver clip around the pituitary stalk, completely occluding any passage through it by tight compression. This was again carried out on dogs. Two out of the three animals subjected by them to this procedure showed postoperative glycosuria. In another, an extreme degree of polyuria persisted for a month. Histologically, the pituitary body showed the same appearances as had been described by Crowe, Cushing and Homans. The pars nervosa was found very cellular with a great increase of hyaline in the tissue spaces.

Karplus and Kriedl [17] were the first to separate the pituitary body from the hypothalamus in monkeys. Two animals lived several weeks without any obvious disturbances. The histological findings were not recorded. In 1911, Morawski [22] divided the pituitary stalk in six more monkeys. Two died within the first day, and of the remaining four which lived from six days to two months, no symptoms were noted. At post-mortem examination of these four animals, the pituitary body was reduced in size, the pars distalis being relatively larger and the pars nervosa smaller than normal. No histological changes were observed in the pars distalis but the pars nervosa showed increased cellularity. He compared his results with those of Biedl who had found in dogs that division of the stalk was as rapidly fatal as hypophysectomy and attributed the untoward experiences with dogs to an involvement of the third ventricle.

Later Bell [3] reported experiments on three dogs. The stalk was compressed in one and divided in two animals. They survived three to four months, all showing adiposity and, in two cases, genital dystrophy and somnolence in addition. Histological examination showed the cells of the pars distalis atrophied and widely separated. Dott [11] in 1923,

repeated the experiment of division of the stalk, introducing a minute platinum plate between the pituitary body and the tuber cinereum in order to ensure the permanent deprivation of the main blood supply of the pars distalis. This procedure was carried out on three dogs. In all cases the characteristic syndrome ensued, viz., lethargy and adiposity, retardation of growth, lowering of temperature and degenerative changes in the thyroid and genital glands. All these symptoms could be attributed to the lack of an adequate blood supply. In addition Dott noticed a severe polyuria most marked during the first twenty-four to forty-eight hours. This he considered dependent upon an irritative stimulus to the pars intermedia by the presence of a foreign body.

In the Cameron lectures (1926), Cushing [10, *b*] reported some further experiments carried out in his laboratory by Maddock. Occlusion of the pituitary stalk by a clip resulted in a post-operative polyuria prolonged in character and a tendency to adiposity. The histological changes were the same as those previously reported in the paper by Crowe, Cushing and Homans.

Method.

The present study was carried out upon twenty dogs and twenty monkeys (*Macaca mulatta*). The ages of the dogs ranged from 6 weeks to 2 years and of the monkeys from 2 to 4 years. They lived in the laboratory in large metabolism cages for two to four weeks before any operative procedure was undertaken. Daily measurements were made of the fluid intake and urinary output. No direct estimation of fluids lost by way of intestines, skin and lungs was made but the "insensible loss" was calculated by computing the difference between the fluid intake and the urinary output. Diets were kept constant throughout the experiment. The basal metabolic rate, the blood-sugar content and the nitrogen and base constituents of the urine were estimated in the monkeys both before and after operation. This was carried out with the collaboration of Dr. N. Rakieten and Dr. M. B. Rheinberger to whom we are indebted.

Operative procedures.—All operations were carried out under sodium amytal anæsthesia given intraperitoneally, 0·5 to 0·6 c.c. of a 10 per cent. solution per kilogram of body-weight. In the monkeys the procedure was as follows:—

A large frontal parietal bone flap extending over the mid-sagittal line was turned down and more room was obtained by enlarging the bony opening deep into the temporal region. The dura was incised in curvilinear fashion parallel to the inferior line of the bone defect and the temporal lobe was carefully elevated. This brought into view the para-pituitary structures of which the oculomotor nerve and the internal carotid artery were the most prominent. Between these, the infundibulum could be clearly seen and a silver clip was applied to the pituitary stalk as far distally from the tuber cinereum as possible, and closed tightly. In three cases, the stalk was divided immediately below

the site of the clip. The minute anatomy of the region varied and in some instances the exposure was improved by gentle retraction of the internal carotid artery forwards. For closure, the bone flap was replaced and the subcutaneous tissues approximated in two layers with interrupted silk sutures. The skin was secured with a continuous subcuticular suture of silk.

In dogs the exposure of the pituitary stalk was also carried out by the subtemporal approach after the zygoma and the temporo-parietal bones were removed on one side. The temporal muscle was employed so as to take the place of a bone flap in the closure. Within twelve hours the animals recovered sufficiently from amytal anæsthesia to begin drinking. During the preceding period of unconsciousness, the dogs passed considerable quantities of urine.

Thyroidectomies were performed in some of the dogs through a midline skin incision and care was taken to leave the parathyroid glands intact. The excised tissue was in all instances verified histologically. On no occasion was there any manifestation of tetany. The animals were surprisingly active after thyroidectomy and showed no gross signs of thyroid deprivation. There was, however, a remarkable and progressive loss of weight after removal of the thyroid.

Histological studies.—The animals were sacrificed at varying periods from three days to ten months after operation. Complete post-mortem examinations were performed on all animals. In half the cases, the tissues were fixed in situ by perfusion of 10 per cent. formol solution and the pituitary bodies were sectioned serially, some in the horizontal and others in the sagittal plane and stained with hæmatoxylin and eosin and Mann's stain. In those cases in which the tissues were not fixed by perfusion with formol, the hypothalamus was fixed in 95 per cent. alcohol and stained by the Nissl method.

Serial sections of the pituitary bodies and hypothalamus in normal monkeys and dogs were treated in a similar manner and served as controls for the histological studies.

Results.

(1) *Metabolic Studies.*

Monkeys.—Occlusion of the pituitary stalk in monkeys did not result in polyuria or polydipsia. The average daily fluid intake and urinary output which before operation varied between 100 c.c. and 200 c.c. remained constantly at this level after operation. In two animals a puncture was made in the tuber cinereum two weeks after the pituitary stalk had been obstructed. In these instances the total daily intake and output rose to 500 c.c. on the first post-operative day, to 900 c.c. on the second post-operative day. It remained at this level for three days and then dropped rapidly to normal.

There was no significant alteration of the basal metabolic rate, the blood-sugar level, or the nitrogen and base constituents of the urine

following occlusion of the pituitary stalk. The respiratory quotient which averaged 0·75 before operation remained constant. Blood-sugar readings ranged between 80 mgm. and 120 mgm. per cent. both before and after operation. The monkeys appeared in perfect health and showed no gross change in body-weight, character of hair, or general activity.

Dogs.—In dogs, occlusion of the pituitary stalk with a silver clip was invariably followed by extreme polyuria and polydipsia, which persisted for several weeks. In a previous communication [21] it has been shown that this effect is abolished by subsequent total thyroidectomy and can be re-established by oral administration of desiccated whole thyroid gland. Alternate states of extreme polyuria and oliguria could thus be produced at will. Total thyroidectomy had no demonstrable effect upon the daily fluid intake and output of the normal dog. In dogs with intact pituitary stalk, thyroid feeding had a mild diuretic action, which was, however, in no way comparable to the extreme polyuria and polydipsia produced by administration of thyroid gland after occlusion of the pituitary stalk. There appeared to be a severe imbalance in the water metabolism of the tissues apart from the renal mechanism in these experiments.

In order to study the effects of occlusion of the pituitary stalk in immature animals, puppies 6 to 7 weeks old were utilized. The procedure was followed by the usual diabetes insipidus, but in addition there occurred marked retardation of growth, sexual infantilism and subsequently extreme adiposity. This is illustrated in the following protocol :—

From a litter of mongrel puppies born in the laboratory, two females were chosen which, after seven weeks were approximately of equal size and weighed 2·7 kgm. and 2·9 kgm. respectively. For the week prior to operation, the average fluid intake for each animal was 400 c.c. daily and the average urinary output 150 c.c. On August 20, 1934, the pituitary stalk of one animal was occluded by means of a silver clip. The other puppy was kept under identical dietary and living conditions as a control. Immediately following operation, the fluid intake rose to 2,200 c.c. daily and remained at a level of 1,600 c.c. for two weeks. It gradually decreased so that after five weeks it ran parallel with the control. The urinary output likewise increased directly after the operation to 1,500 c.c. and averaged about 1,200 c.c. daily for two weeks, falling gradually to the control level, so that after five weeks there was no further evidence of diabetes insipidus.

Although during the first ten weeks after operation there was no perceptible difference in the rate of growth of the two animals and the body-weights were

approximately the same, five months after operation there was a marked disproportion in size and weight. The control litter mate weighed 10·8 kgm. The operated animal was considerably dwarfed in comparison and weighed only 6·4 kgm. It showed a slight tendency to adiposity and its coat was longer and of finer texture than that of its sister. Its head was small and the expression placid and mature and the animal showed none of the playful activity of the other puppy. From this time it became very markedly adipose and, though remaining dwarfed, gradually approached the body-weight of the control. Ten months after operation it weighed 12 kgm. while the control weighed 12·7 kgm. (fig. 1). On June 5, 1935, both animals were sacrificed for

FIG. 1.—Littermate female puppies aged 12 months, to show dwarfism and adiposity ten months after occlusion of the pituitary stalk. Control animal on left.

histological purposes. There were no abnormal findings in the control dog In the litter mate which had been operated upon, the most striking features apart from the changes in the pituitary body were the degree of adiposity and the genital infantilism. The subcutaneous fat, for instance, even over the sternum, measured 2·5 cm. in thickness. There was extreme hypoplasia of the uterus, vagina and ovaries.

Horizontal serial sections of the pituitary body showed disorganization of structure of the glandular part with marked decrease in the vascularity. On close examination the cells showed no granular formation in the cytoplasm. The cell outlines in many parts appeared to fuse. This glandular tissue with an incomplete lining of ciliated epithelium constituted the wall of a large central cavity. There were many small cysts of the same nature lying

peripheral to the central cyst within which lay fragments of degenerated cells which had lost their nuclei. The pars nervosa appeared normal according to all criteria.

(2) *Histological Studies.*

In the monkey the pituitary body showed no real change in size or in the cyto-architecture of the glandular elements (fig. 2.) The vascularity of the pars distalis and pars tuberalis was unimpaired as seen in carmine gelatine preparations after the pituitary stalk had been clipped. The pars nervosa was not altered in size and was normal in appearance except for some increased cellularity which varied from case to case. The demonstrable colloid content did not vary appreciably from the normal.

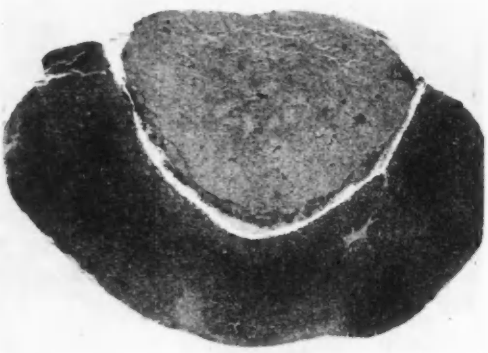

FIG. 2.—Horizontal section of primate pituitary body, two and a half months after occlusion of the pituitary stalk. No demonstrable alteration from the normal. (Mag. × 25.)

In dogs in which the pituitary stalk had been clipped there was an astonishing appearance for comparison (fig. 3). The pituitary body was not the normal pink round structure, but a flattened buff-coloured organ which was very friable and when ruptured, discharged a drop of oily brown fluid leaving a collapsed cystic shell. Microscopically, the wall of the cyst consisted of necrotic cells of the pars distalis, islets of cells remaining visible near the periphery where the blood supply appeared to be adequate. The carmine gelatine preparations showed almost complete avascularity of the tissues except in the peripheral parts where small blood-vessels were to be seen. The cysts had in part epithelial linings which were ciliated in some instances. The contents of he cyst appeared microscopically to be composed of débris and

degenerated cells. In some cases no pars nervosa tissue could be recognized, while in others portions of the pars nervosa were found and, apart from some increased cellularity, showed no appreciable difference from the control. As in the monkey, there was no increase in colloid-like material in the glandular or nervous portions of the pituitary body.

The histological changes in the hypothalamus after occlusion of the pituitary stalk were similar in the dog and the monkey. The nuclei of the cells of the supra-optic and paraventricular nuclei showed the characteristic eccentricity, but not the shrinkage and hyperchromatosis diagnostic of retrograde cell change. The cytoplasm was pale with chromatin granules gathered at the periphery. Such an appearance,

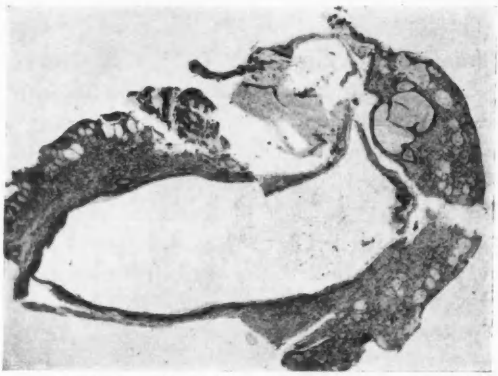

FIG. 3.—Section of canine pituitary body three months after occlusion of the pituitary stalk. Extensive degenerative changes. (Mag. × 25.)

however, is frequently seen in the normal. Interspersed among the neurones were a larger number than usual of glial cells, often found in clusters surrounding the ganglion cells. Some of the latter appeared as merely shadowy forms, suggestive of degeneration. No demonstrable changes were observed in the tuberal or mammillary nuclei.

DISCUSSION.

Experimental occlusion of the pituitary stalk as carried out in the present investigation accomplishes the complete obstruction to: (*a*) the pathway of secretion from the pituitary body to the hypothalamus along the stalk, either through the tissue spaces of the nervous portion or by way of the suggested portal circulation in the glandular part; (*b*) the

transmission of impulses along the nerve connections in the stalk; and (*c*) the blood supply of the pituitary stalk reaching it along or in the stalk.

In the above experiments, occlusion of the pituitary stalk in the monkey resulted in no clear physiological evidence of failure of the pituitary hormones to reach the general circulation. This, together with the complete absence of any histological changes in the pituitary body in this animal is indicative that in the monkey at least, the passage of secretion along the stalk, if any, is not of great significance. This does not disprove the theory that the pituitary principle acts on hypothalamic centres, for it may still do so by means of the general circulation.

The existence of a bundle of unmyelinated fibres from the supra-optic and tuberal nuclei along the stalk into the pars nervosa seems to be fairly well established from the work of Ramon-y-Cajal [25], Hoenig [15], Tello [29], Trautmann [30], Pines [24], and Greving [14]. This tract is not well developed in the monkey. The fine thread-like nature of the stalk and the sparseness of nerve fibres passing along it do not suggest any striking neural connections between the pituitary body and hypothalamus. That such a tract activates the pars intermedia is still doubtful, and evidence in support of this view is lacking. The recent work of Karplus and Peczenik [18] is not wholly conclusive. After division of the pituitary stalk there are cellular changes in the supra-optic and paraventricular nuclei in some instances, but the changes consisting of pallor of some of the cells with a slight glial reaction around others, are difficult to interpret, for eccentricity of the nucleus and chromatolysis are no criteria of axonal division in the supra-optic and paraventricular nuclei.

In the present investigation the rich vascularity of the glandular portion in the monkey following occlusion of the stalk contrasted markedly with the almost complete avascularity and extensive necrotic changes of the corresponding part in the dog following this procedure. It is clear from these studies that clipping of the stalk occludes the major blood supply to the pituitary body in the dog and does not do so in the monkey. This accounts adequately for the retardation of growth and sexual infantilism observed in puppies and is in accordance with the view of Paulesco and Crowe, Cushing and Homans who described division or occlusion of the pituitary stalk in the dog as equivalent to a "complete or almost complete" hypophysectomy.

The reason for the difference in response of the water metabolism

in the dog and monkey is not as clear. The results can be explained in one of two ways. The diabetes insipidus might be attributed to a lack of antidiuretic principle owing to degeneration of the pituitary of the dog. Such a view would be in accordance with all the histological findings in the present study. Hypophysectomy, however, has not been followed by diabetes insipidus in either the dog or the monkey, and in the latter, in the experience of the authors, hypothalamic lesions *after* previous hypophysectomy have resulted in severe upset of the water metabolism. Similarly, in the dog *after* hypophysectomy, Camus and

FIG. 4.—Coronal section of hypothalamus and proximal part of pituitary stalk in the monkey to show the pars tuberalis imbedded in the substance of the tuber cinereum. (Mag. × 100.)

Roussy have produced diabetes insipidus by a small lesion in the tuber cinereum. If, as Richter maintains, the essential and only factor necessary for the production of diabetes insipidus is a lesion severing the connection between the "posterior lobe" and the nuclei of the brain stem, provided that some "anterior lobe" tissue remains, then there is no clear explanation why the secondary lesion in the tuber cinereum after a previous hypophysectomy should be followed by polyuria. The fact that, in the monkey at least, the pars tuberalis spreads out under the tuber cinereum and is actually imbedded in the substance of this

part of the hypothalamus (fig. 4) is of great importance in this problem, for a complete hypophysectomy (including the pars tuberalis) is obviously impossible without destruction of the tuber cinereum. In view of this

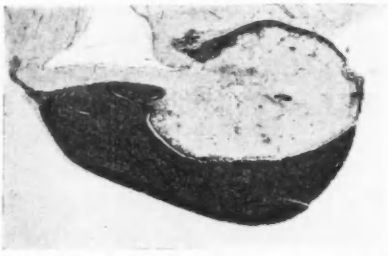

FIG. 5.—Sagittal section of canine pituitary-hypothalamic block injected with carmine gelatine mass, showing the short thick pituitary stalk containing direct prolongation of the third ventricle. (Mag. × 17.)

FIG. 6.—Sagittal section of the pituitary-hypothalamic block of the monkey injected with carmine gelatine mass, showing the long thread-like nature of the pituitary stalk. The third ventricle does not extend beyond the tuber cinereum. (Mag. × 25.)

fact the clear distinction drawn between hypophysectomy and a strictly hypothalamic lesion by earlier workers in this field is not feasible and many of their conclusions cannot therefore be accepted as absolute.

The second explanation which might be offered for the extraordinary

difference in the behaviour of the fluid exchange in the dog and the monkey is injury to hypothalamic centres. There is an important anatomical difference in this region in the two species. In the dog the pituitary stalk is short, thick, and contains a direct prolongation of the third ventricle, so that in this animal the stalk and tuber cinereum are identical (fig. 5). In the monkey, on the other hand, the stalk is comparatively a long thread-like band connecting the clearly differentiated tuber with the pituitary body, and the relations are such that it is possible to place a silver clip around the stalk without injuring the adjacent structures (fig. 6). Furthermore, in this animal, the third ventricle ends in the tuber cinereum proper and does not extend into the stalk. In the dog, therefore, the lower hypothalamic centres are damaged somewhat by the silver clip and are certainly not involved in the monkey. Such an explanation would appear to fit all the known facts, although it still leaves unexplained the anti-diuretic action of pituitrin on experimental diabetes insipidus.

Summary.

1. Complete obstruction to the passage of secretion and nerve impulses between the pituitary body and hypothalamus was accomplished by the application of a silver clip to the pituitary stalk in the dog and the monkey.

A striking difference was subsequently observed in the two species.

2. Whereas in the dog there followed a state of diabetes insipidus which was abolished by thyroidectomy and re-established by oral administration of thyroid gland, no polyuria or polydipsia occurred in the monkey. The hypothesis of Fisher, Ingram and Ranson is therefore not applicable to the latter animal.

3. The basal metabolic rate, the blood-sugar level and the nitrogen and base constituents of the urine were unaltered in the monkeys.

4. Metabolic changes were manifested in puppies by retardation of growth, sexual infantilism, adiposity, refinement of hair and sluggish general behaviour.

5. The canine pituitary showed marked degenerative changes due to interference in the major blood supply as revealed by carmine gelatine preparations. No comparable changes either in vascularity or in cyto-architecture were demonstrable in the primate pituitary.

6. There is an important anatomical difference in the pituitary stalk and in the downward extension of the third ventricle in the two species.

7. It is concluded that in the monkey obstruction of the pituitary stalk does not interfere with the nourishment of the pituitary body or with discharge of the pituitary hormones into the general circulation.

8. The metabolic responses in the dog have been attributed in the past either to a pituitary or to a hypothalamic disturbance, but the inseparable anatomical arrangement of the pituitary-hypothalamic complex does not warrant such a clear distinction on experimental grounds. In the monkey the evidence supports the hypothalamic origin of diabetes insipidus.

REFERENCES.

[1] Aschner, B. (*a*) "Ueber die Funktion der Hypophyse," *Arch. f. d. ges. Physiol.*, 1912, **146**, 1-146; (*b*) "Hypophyse und Diabetes Insipidus," *Münch. med. Wochenschr.*, 1917, **64**, 81.

[2] Bailey, P., and Bremer, F. "Experimental Diabetes Insipidus," *Arch. Int. Med.*, 1921, **28**, 773-803.

[3] Bell, W. B. "The Pituitary," New York, 1919.

[4] Biggart, J. H. "Diabetes Insipidus," *Brain*, 1935, **58**, 86-96.

[5] Bourquin, H., Benesh, L., and Lanam, M. "Studies on Diabetes Insipidus. I." *Amer. Journ. Physiol.*, 1927, **79**, 362-376.

[6] Bourquin, H. "Studies on Diabetes Insipidus. II." *Ibid.*, 1927, **83**, 125-133; "Studies on Diabetes Insipidus. III." *Ibid.*, 1929, **88**, 519-528; "Studies on Diabetes Insipidus. IV." *Ibid.*, 1931, **96**, 66-77.

[7] Camus, J., and Roussy, G. (*a*) "Présentation de sept chiens hypophysectomisés depuis quelques mois," *Compt. Rend. Soc. Biol.*, 1913, **74**, 1386-1388; (*b*) "Diabète insipide expérimental." *Ibid.*, 1920, **83**, 764-765, 901-902, 1578-1583; (*c*) "Experimental Researches on the Pituitary Body," *Endocrinology*, 1920, **4**, 507-522; (*d*) "Les fonctions attributées à l'hypophyse," *Journ. d. Physiol. et de Pathol.*, 1922, **20**, 509-518, 535-547; (*e*) "Les syndromes hypophysaires," *Rev. Neurol.*, 1922, **29**, 622-637.

[8] Crowe, S. J., Cushing, H., and Homans, J. (*a*) "Effects of Hypophyseal Transplantation Following Total Hypophysectomy in the Canine," *Quart. Journ. Exper. Physiol.*, 1909, **2**, 389-400; (*b*) "Experimental Hypophysectomy," *Bull. Johns Hopkins Hosp.*, 1910, **21**, 127-169.

[9] Cushing, H., and Goetsch, E. "Concerning the Secretion of the Infundibular Lobe of the Pituitary Body and its Presence in the Cerebrospinal Fluid," *Amer. Journ. Physiol.*, 1910, **27**, 60-86.

[10] Cushing, H. (*a*) "Concerning Diabetes Insipidus and the Polyurias of Hypophyseal Origin," *Bost. Med. and Surg. Journ.*, 1913, **168**, 901-910; (*b*) "Studies on Intracranial Physiology and Surgery," Oxford University Press, London, 1926, 1-146; (*c*) "Papers relating to the Pituitary Body, Hypothalamus and Parasympathetic Nervous System," Thomas, Springfield, 1932, 1-234; (*d*) "Posterior Pituitary Activity from an Anatomical Standpoint," *Amer. Journ. Path.*, 1933, **9**, 539-547.

[11] Dott, N. M. "An Investigation into the Functions of the Pituitary and Thyroid Glands," *Quart. Journ. Exper. Physiol.*, 1923, **13**, 241-282.

[12] Fisher, C., Ingram, W. R., and Ranson, S. W. "Relation of Hypothalamico-hypophyseal System to Diabetes Insipidus," *Arch. Neur. and Psych.*, 1935, **34**, 124-163.

[13] Gemelli, A. (*a*) "Sur la fonction de l'hypophyse," *Arch. Ital. de Biol.*, 1908, **50**, 157-174; (*b*) "Ulteriore contributo alla fisologia dell' ipofisi," *Folia. Neurobiol.*, 1908, **2**, 167-196.

[14] GREVING, R. (*a*) "Zur Anatomie, Physiologie und Pathologie der vegetativen Zentren im Zwischenhirn," *Ergebnisse der Anatomie und Entwicklung*, 1923, **24**, 348-413; (*b*) "Beiträge zur Anatomie der Hypophyse und deren Funktion," *Deutsch. Zeitschr. f. Nervenheilk.*, 1926, **89**, 179-194; (*c*) "Beiträge zur Anatomie der Hypophyse und deren Funktion." II. Mitteilung. *Zeitschr. f. d. ges. Neur. u. Psychiat.*, 1926, **104**, 466-479.

[15] HOENIG, C. "Untersuchungen zur Histologie der Hypophyse," *ibid.*, 1922, **79**, 197-209.

[16] HOUSSAY, B. A. "The Pituitary Body and Polyuria," *Endocrinology*, 1918, **2**, 94-97.

[17] KARPLUS, J., and KRIEDL, A. "Operationen am überhängenden Gehirn," *Wiener klin. Wochnschr.*, 1910, **23**, 309-310.

[18] KARPLUS, J. P., and PECZENIK, O. "Uber die Beeinflussung der Hypophysentätigkeit durch die Erregung des Hypothalamus," *Arch. f. d. ges. Physiol.*, 1930, **225**, 654-668.

[19] LESCHKE, E. "Diabète insipide et système hypothalamo-hypophysaire," *Ann. de Méd.*, 1933, **33**, 261-271.

[20] LHERMITTE, J. "La polyurie infundibulaire, le diabète insipide syphilitique," *ibid.*, 1922, **11**, 89-127.

[21] MAHONEY, W., and SHEEHAN, D. "The Effect of Total Thyroidectomy upon Experimental Diabetes Insipidus in Dogs," *Amer. Journ. Physiol.*, 1935, **112**, 250-255.

[22] MORAWSKI, J. "Die Durchtrennung des Hypophysenstieles beim Affen., *Zeit. f. d. ges. Neur. u. Psychiat.*, 1911, **7**, 207-218.

[23] PAULESCO, N. C. "L'Hypophyse du Cerveau," Paris, 1908.

[24] PINES, J. (*a*) "Ueber die Innervation der Hypophysis cerebri" (Mit. I), *Journ. f. Psychiat. u. Neurol.*, 1925, **32**, 80-88; (*b*) "Ueber die Innervation der Hypophysis cerebri" (Mit. II), *Zeit. f. d. ges. Neur. u. Psychiat.*, 1926, **100**, 123-138; (*c*) "Ueber die Innervation der Hypophysis cerebri," *ibid.*, 1927, **107**, 507-511.

[25] RAMON-Y-CAJAL, S. "Estructura del ganglio de la habenula de los mamiferos," *An. Soc. Españ. Hist. Nat.*, 1894, S. 2, **23**, 185-237.

[26] RICHTER, C. P. (*a*) "Experimental Diabetes Insipidus," *Brain*, 1930, **53**, 76-85; (*b*) "Experimental Diabetes Insipidus: its relation to the Anterior and Posterior Lobes of the Hypophysis," *Amer. Journ. Physiol.*, 1934, **110**, 439-447.

[27] ROUSSY, G., and MOSINGER, M. "Le tuber cinereum et son rôle dans les principales fonctions du metabolisme," *Ann. de Méd.*, 1933, **33**, 193-238.

[28] STAEMMLER, M. "Diabetes Insipidus und Hypophyse," *Ergebn. d. allg. Path. u. path. Anat.*, 1932, **26**, 59.

[29] TELLO, F. "Algunas observationes sobre la histologiá de la hipófisis humana," *Trab. d. lab. de invest. biol. Univ. de Madrid*, 1912, **10**, 145-183.

[30] TRAUTMANN, A. "Anatomie und Histologie der Hypophysis cerebri einiger Säuger," *Arch. f. mik. Anat.*, 1909, **74**, 311-367.

[31] VASSALE, G., and SACCHI, E. "Sulla distruzione della gliandola pituitaria," *Riv. sper. di Freniat. Reggio-Emilia*, 1892, **18**, 525-561.

THE EFFECTS OF LESIONS OF THE DORSAL COLUMN NUCLEI IN THE MACACUS RHESUS.

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I.—Introduction.

As a sequel to the findings which we have reported in this Journal [1, 2] on the effects of section of the dorsal columns and the restiform body, we are now presenting a report of the effects of lesions of the gracile and cuneate nuclei as the next step in an analysis of sensory and cerebellar pathways.

II.—Review of the Literature.

There are relatively few reports of experiments dealing with the effects of lesions of the gracile and cuneate nuclei. Bechterew (1890) [3] noted a severe disturbance of equilibrium in a few dogs in which he made wounds in these nuclei. The dogs showed lateropulsion with falling. The disturbance was greater when the animals were blindfolded. No sensory abnormalities were described.

Ferrier and Turner (1894) [4] described the behaviour of monkeys in which they destroyed both gracile and cuneate nuclei. When the nucleus gracilis or clavate nucleus of one side was destroyed the animal showed a tendency to fall backward to either side; there was considerable swaying on exertion, and in walking the limb movements were slightly sprawling. The head was retracted and the chin was turned to the side of the removal. The knee-jerks were active and equal. Examination revealed complete retention of the sensibility to touch, pain and localization. One week after operation the animal was reported as being difficult to distinguish from a normal monkey. It jumped and climbed readily. Histological controls of the lesions were described.

F. W. Mott (1895) [5] reported experiments on monkeys in which he cut the afferent fibres on one side as they left the gracile and cuneate nuclei. He reported difficulty in observing the physiological effects, but he stated that extensive lesions were associated with inability of the animal to use the ipsilateral limbs, and with diminution of sensation on

the side of the lesion. W. A. Turner (1895) [6] reported on the localized destruction of the tubercle of Rolando in five monkeys. We mention his findings because of the fact that the cuneate nucleus was usually included in the lesions. None of the clinical manifestations was attributed by the author to the involvement of the cuneate nucleus.

Tschermak (1898) [7] studied the effects of lesions of the dorsal column nuclei in cats. In three animals he destroyed these nuclei on one side. By the first or second day after the operation they made attempts to walk, in which attempts, however, they swayed and fell toward the side of the lesion, particularly if they attempted to raise the feet. Later, the animals did not fall toward the involved side but could be easily pushed over on to that side. In walking the contralateral limbs were used firmly, but the ipsilateral legs were considerably abducted, and the fore-foot was used clumsily and was often placed with the dorsum downward. On sitting up all three animals swayed toward the side of the operation. There were no disturbances of touch, pain and localization. All the symptoms decreased rapidly and after two, or at most five days, they had practically disappeared. In one case, however, there was a noticeable disability even up to death after sixteen days. The author felt that many of the symptoms observed by him could be accounted for by a disturbance of the sense of position and of movement of the limbs, i.e. of the so-called muscle sense. Serial sections of the material revealed destruction of the posterior two-thirds of the dorsal column nuclei of one side. The substantia gelatinosa was also involved in the lesion, and the nucleus of the 12th nerve was usually destroyed. In the caudal portion of the wound the dorsal as well as the most cephalic portions of the pyramidal decussation were injured. Above the lesion the restiform body and the lemniscus were degenerated.

Probst (1902) [8] reported on the effects of lesions of the dorsal column nuclei in dogs and cats. He compared the effects of such lesions to those resulting from lesions of the cerebellum. Following a right-sided lesion of the nuclei, the dog fell to the left and presented ataxia and disturbances in equilibrium. There was also a tendency to fall over backwards. In the acute phase the dog maintained the ipsilateral fore-limb in tonic flexion and often placed the limb on the floor with the dorsum downwards. Because of the tonic flexion the fore-limbs were often crossed. Some degree of paresis of the ipsilateral fore-limb persisted even to the 15th day. According to the author such paresis

resembled that following removal of the cortical motor area and was based upon a loss of muscle sense. The pupils did not react well. The knee-jerks were active. The dog did not react to pin-pricks.

Mussen (1927) [9], in reporting on cats in which the nuclei graciles et cuneati were cauterized, claimed that the characteristic symptom was a loss of the postural sense involving joints of one or more limbs. Equilibrium was but slightly disturbed and pain and touch sensation were normal. In one case with right-sided destruction of the nuclei loss of sense of position was indicated by the animal frequently resting on the dorsum of the right fore-limb. Any abnormal posture in the hind limbs would be corrected at once. In his cases the disabilities, which were interpreted as indicating loss of sense of position, had not disappeared at the end of three weeks. Unfortunately we have not been able to find descriptions of the exact extent of the lesions in his cases.

III.—Method in our Experimental Work.

Macacus rhesus monkeys were used in all the experiments. In all twenty-one animals were used. The operations consisted of unilateral or bilateral destruction of the gracile and cuneate nuclei, unilateral destruction of the nucleus gracilis or of the nucleus cuneatus, and lesions of these nuclei in combination with other lesions, e.g. of the spino-cerebellar tract or the inferior cerebellar peduncle.

The monkey was placed in position on the table so that the head and neck extended over the end of the table, enabling the operator to flex the head on the chest. Under deep ether anæsthesia, with usual surgical aseptic technique, the muscles of the neck were split in the mid-line and held apart with an automatic retractor. The occipital bone was cleared of muscular attachments and the arch of the atlas was exposed. The occipital bone was removed well up over the transverse sinuses. Usually the arch of the atlas was removed. The occipito-atlantoid ligament and the dura over the cerebellum were split and retracted, exposing the caudal portion of the vermis, portions of the lateral cerebellar lobes and the upper portion of the spinal cord. The arachnoid was opened and the region of the obex carefully cleared of attachments of arachnoid. The vermis was retracted upward with a small flat retractor and the nuclear groups could then be clearly seen. The various lesions were made usually with a small ophthalmic knife or capsulotome, which made it possible to cut out a small mass of tissue which was then removed with fine forceps and eye scissors. In a few cases the lesion was made with a small sharpened Spratt's curette, or with a hot needle and finally in one or two cases by injecting a drop or two of alcohol with a 25 gauge bent needle. The dura was not sutured in closing. The muscles were approximated with catgut or black silk sutures and

the wound was closed with Michel skin clips. With this simple technique we experienced no difficulty in any of our animals, as regards either infections or marked spreading of the lesion, except in the widely destructive lesions involving both gracile and cuneate nuclei. It is of interest that out of five animals in which the complete bilateral lesion was attempted at one stage, three died after an apparently normal recovery up to three days when they suddenly became ill and usually died on the fourth day. Post-mortem examinations revealed pneumonia in all cases. The lesion probably had spread to involve the nuclei of the vagus. The animals with smaller surgical lesions or complete unilateral involvement were usually up and about the cage in an hour, or at most two hours, after the operation. The two animals which survived complete bilateral lesions were very weak for three or four days after the operation, but once they passed this point they improved rapidly.

The animals were usually killed for study with the Marchi or the Weigert stains, the Marchi stain requiring sacrifice of the animal from the eleventh to the sixteenth day and the Weigert requiring at least six weeks survival. Serial sections of the brain-stem frontal to the upper cervical cord were studied in each of these animals with one or other of these methods. A complete anatomical report of the degenerations resulting from these lesions will be reported elsewhere in a study of the connections of the posterior column nuclei. In the present paper, we are concerned mainly with the symptoms following the various experiments and with a presentation of the essential features of the anatomical lesions.

IV.—Experimental Material.

In all, twenty-one monkeys were used in these operations on the dorsal column nuclei. The protocols to be presented will include one of each of the various pure types: (*a*) Unilateral destruction of the nucleus gracilis and the nucleus cuneatus; (*b*) unilateral destruction of the nucleus gracilis; (*c*) unilateral destruction of the nucleus cuneatus; (*d*) bilateral destruction of the nuclei graciles et cuneati.

Protocol No. 1.—Cer. 57.

Operation, November 22, 1932: Destruction of the right dorsal column nuclei.—Usual technique as described above. Very little bleeding. The lesion appeared well confined to the nuclei at operation. When the animal came out of the anæsthesia there was a sharp twist of the chin to the right, but no other abnormality.

Three hours after operation.—The animal is now well out of the anæsthesia and is sitting up in the cage eating a piece of orange. The rotation of the chin to the right which was present for about one hour after the operation has disappeared and the posture of the head is now normal. The animal usually sits with the right side of the body against the cage. When it sits on

the floor without the support of the cage it shows a slightly flexed and adducted posture in the right fore-limb with some abduction in the right hind-limb giving a broad base to the hind-limbs. In this sitting posture there is no side-to-side swaying of the animal. If it is teased with a small stick it reaches out and takes the stick with the left hand only, no grasping efforts being made with the right limbs. There is no abnormality in the reactions of the eyes nor spontaneous nystagmus. No evidence of facial paralysis, or any signs of vestibular dysfunction are observed. The animal seems to be able to swallow and to protrude the tongue. In the sitting posture the most definite disability at this time seems to be a marked loss of spontaneous use of the right limbs. The disability seems to be of the same type as that seen in lesions of the dorsal columns and consists of hypotonia and a lack of spontaneous grasping, but the deep reflexes are active. All of the disabilities are more accentuated in the right fore-limb, which remains practically unused in movements of locomotion, reaching, climbing or in any type of movement requiring spontaneous activity with the limb. The right hind-limb is held slightly flexed, but it is used awkwardly in walking, with jerkiness and lack of co-ordination. It is not employed, however, for active grasping. The gait is practically three-legged, since the right fore-limb is not used. At times the animal rests on the right fore foot with the dorsum of the foot downward. In climbing the animal uses the left limbs practically alone. Gross attempts at catching hold of the support, however, are made with the right limbs, particularly the hind-limb, but the animal seems to be unsuccessful in actually grasping firmly the cage or object of support. Muscle tone diminished in both right limbs. The hypotonia is greater in the fore-limb. So far as can be determined at this stage there does not seem to be any loss of response to pain or touch or of localization of touch. When the animal is dropped head first with the eyes open there is some extension of all limbs, but the right fore-limb is extended much less actively than the left fore-limb. The left limbs appear normal. The hopping and placing reflexes are diminished on the right. The vestibular or labyrinthine reflexes are normal.

November 23: twenty-four hours after operation the condition was unchanged. It is of interest to note here how this animal differs at this stage from animals at a similar stage with lesions of the spino-cerebellar system in the medulla. This animal shows absence of spontaneous grasping and active deep reflexes, in contrast to the normal grasping and hypo-reflexia of the spino-cerebellar animal. In addition, no falling toward the side of the lesion occurs, whereas this is the usual finding when the spino-cerebellar tracts are divided.

November 29: One week after operation. The animal has improved considerably during the past week, but the phenomena which were present at the three hour-stage persist, though slightly less intense. The only sensory abnormality which can be determined is the response of the animal to passive movement of the limbs when the eyes are covered. Then it makes no attempt to correct changes in the position of the right limbs, whereas vigorous attempts are made when the left limbs are moved. When the animal runs, jumps

about, or climbs along a pipe or a bar, the disability in the right side becomes clearer. It consists essentially of the animal's inability to use the right limbs for actively grasping the object of support. At times the right fore-limb is used for encircling the support with the upper portions of the extremity, but the object is never grasped spontaneously with the fingers or hand. It is of interest, however, that if the hand is placed around a small bar and the animal is then suddenly allowed to drop while blindfolded, it may grasp the bar and remain hanging for a considerable time, showing that a reflex type of grasping may occur in the involved limbs. Testing of vestibular function, done with Dr. Northington,

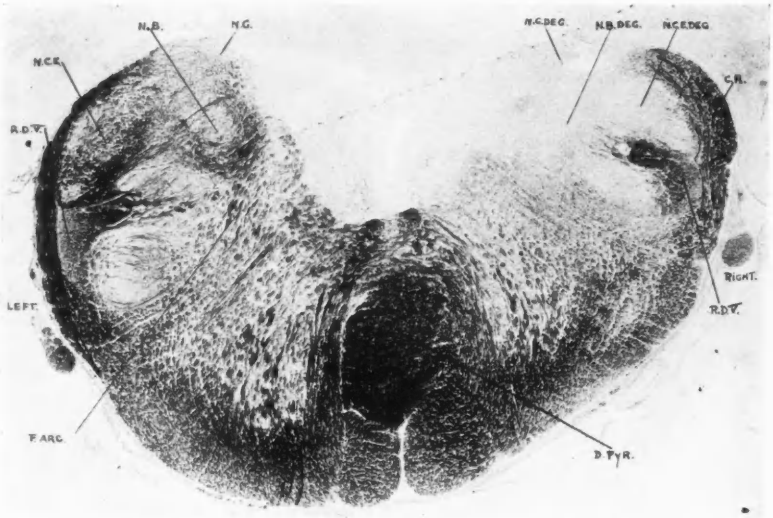

FIG. 1.—Section of medulla at level of pyramidal decussation. Weigert preparation. On the right there is seen to be a complete disappearance of the nucleus gracilis, the nucleus cuneatus and the dorsal portion of the external cuneate nucleus, all of which have been replaced by degenerated tissue. There is a complete absence of arcuate fibres from the nuclei on the right side. The section is somewhat oblique, the dorsal portion being at a more cephalic level than the ventral. N.G., nucleus gracilis; N.B., nucleus cuneatus; N.C.E., external cuneate nucleus; R.D.V., descending root of the 5th nerve; F.Arc., arcuate fibres; D.Pyr., pyramidal decussation; C.R., corpus restiforme; Deg. (after initials), degenerated.

shows no evidence of involvement of the vestibular apparatus. The swimming of the animal appears unaffected.

December 6: Two weeks after operation the condition was the same.

December 22: One month after operation. The animal has improved considerably. However, on careful examination it is seen to present essentially the same disabilities as were present at the earlier stage. The right fore-limb, for example, is practically never used for active grasping movements such as for picking up food; at the most it is employed in gross supporting movements.

A slightly flexed posture and some degree of hypotonia still persist. The right hind-limb has improved and is used quite well in walking, but occasionally the toes may be turned under the sole of the foot without any attempt on the part of the animal to correct the posture. Extension of the limb on falling, and the placing and hopping reflexes have improved considerably. There is no clinical evidence of vestibular dysfunction. At this stage the essential deficiencies are in the ability for active accurate grasping with the right limbs, especially with the fore-limb and diminution of the sense of position. This is a picture closely resembling that seen in right sided hemisection of the dorsal columns in the high cervical region.

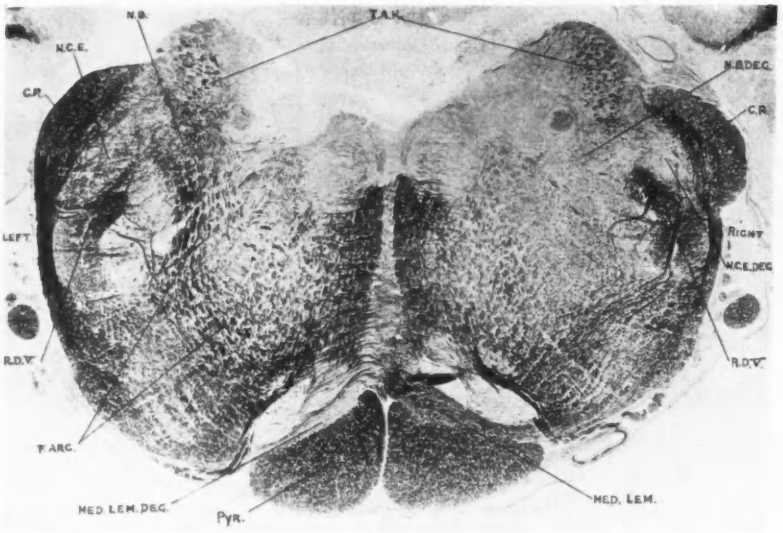

FIG. 2.—Section of the medulla from the same animal as fig. 1 at a higher level. Weigert preparation showing degeneration of the nucleus cuneatus and the external cuneate nucleus on the right with disappearance of the internal arcuate fibres and degeneration of the left medial lemniscus. The I.A.K. bundles are seen to be well preserved on both sides. The section is somewhat oblique, the dorsal portion being at a more cephalic level than the ventral. I.A.K., juxtarestiform bodies; N.B., nucleus cuneatus; N.C.E., external cuneate nucleus; C.R., corpus restiforme; R.D.V., descending root of the 5th nerve; F.Arc., arcuate fibres; Med. Lem., medial lemniscus; Deg. (after initials), degenerated.

January 22, 1933: Two months after operation. The animal remains essentially stationary, still showing the same deficiencies.

February 22: Three months after operation, the condition was the same.

May 22: Six months after operation. The disinclination to use the right arm in reaching for food, in climbing, or in any type of the finer spontaneous grasping movements has persisted up to the present. Definitely co-ordinated movements of the fingers are not observed. The right hind-limb is used to considerable

advantage, although here again the finer grasping movements are not well performed. Muscle tone is still diminished on the right side. The deep reflexes are active. No sensory defects are found except a failure to respond promptly to change in position of the right limbs. The animal was killed at this chronic stage for study with the Weigert stain.

Anatomical Report.—Serial sections with the Weigert stain revealed complete destruction of the nucleus gracilis and nucleus cuneatus on the right side and some cicatricial involvement of the nucleus gracilis on the left. This was not marked, however, and was confined to the dorsal portion of the nucleus.

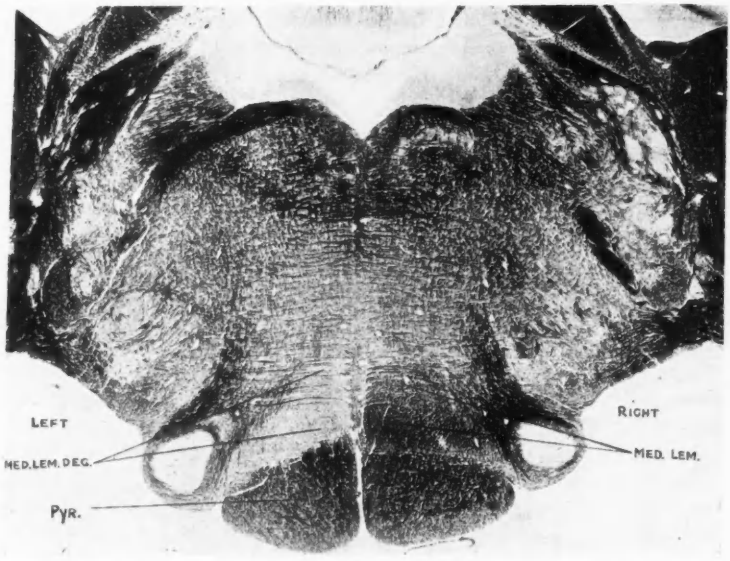

FIG. 3.—Section of the medulla from the same case as figs. 1 and 2, but at a considerably higher level, showing the complete degeneration of the medial lemniscus on the left. Weigert preparation. Med. Lem., medial lemniscus; Pyr., pyramid; Deg. (after initials), degenerated.

On the right, the lesion had involved all elements of the nuclei gracilis et cuneatus in addition to a portion of the external cuneate nucleus (nucleus of Clarke-Monakow) (figs. 1 and 2). On this side the absence of arcuate fibres, due to destruction of their nuclei of origin, was in marked contrast with the left side, where the intact arcuate fibres could be clearly seen. Sections in the spinal cord below the lesion showed no degeneration in the pyramidal tracts. Above the lesion (fig. 3) there was a complete degeneration of the left medial lemniscus which arose from the right nuclei gracilis et cuneatus. Because of the involvement of Clarke-Monakow's nucleus on the right, the restiform body above the lesion appeared slightly paler than did the normal left side. The vestibular

nuclear system and the I.A.K. system (juxtarestiform body) appeared well preserved on both sides.

In summary, the case anatomically presents a complete destruction of the right nuclei gracilis and cuneatus and of a portion of Clarke-Monakow's nucleus, with degeneration in the opposite medial lemniscus owing to destruction of the first two nuclei. There is also slight involvement of the left nucleus gracilis.

Protocol No. 2—Monkey Cer. 139.

Operation, January 4, 1934 : Lesion of the left nucleus gracilis.—On coming out of the anæsthesia there was no abnormal posture of the head or limbs.

Three hours after operation.—With the animal well out of the anæsthetic there is very little abnormal in its behaviour. The most important finding at this time is a slight weakness on the left side with relative disuse of the left limbs, especially in active grasping movements. The involvement in the left fore-limb is very slight and inconstant. The left hind-limb is used but appears clumsy. At times when the animal sits up, the left hind-limb is abducted and the toes of the left hind foot occasionally turn in under the foot without the animal appearing to notice it. The animal uses both fore-limbs in reaching for food, although slight preference is given to the right. Muscle tone is diminished in the left hind leg. The knee-jerks are active on both sides, possibly slightly more active on the left. All the special reflexes, including the righting, position and labyrinthine reflexes are normal, except the hopping and placing reflexes which are somewhat diminished in the left hind-limb. The animal responds to pinching, deep pressure and superficial touch in all the limbs and the trunk and head. It appears to be aware, when blindfolded, of changes in the position in all limbs except in the left hind-limb in which relatively greater excursions can be made without apparent awareness by the animal. When the animal jumps from a high place the left hind-limb tends to slip on landing. On climbing there is very little disability, apart from a slight clumsiness or awkwardness and failure to place the left hind-limb accurately. The more the animal climbs about now the more exact it becomes with the left fore-limb. The effect on this limb is merely temporary.

To summarize, in the acute stage we find an inco-ordination and some diminution in the sense of position in the left hind-limb, associated with a diminution in muscle tone, retention of sensation, diminution in hopping and placing reflexes, and an active knee-jerk. There is a slight involvement of a similar kind in the left fore-limb.

January 5, 1934.—Twenty-four hours after operation. The condition is unchanged except that the involvement of the left fore-limb seems to have completely disappeared. The animal now uses both fore-limbs indiscriminately for picking up food, for climbing, or catching flies.

January 11.—One week after operation. During the past week the animal has improved so much that, except for slight instability of the left hind leg in climbing, diminution in the hopping reflex response, slight weakness in jumping and some hypotonus and active deep reflexes in this limb, the animal appears normal. Both fore-limbs have been equally well used in reaching for food.

January 15.—Eleven days after operation. The condition of the animal is essentially the same. The animal was killed on this date for study by serial Marchi preparations.

Anatomical Report.—The lesion was confined essentially to the nucleus gracilis on the left. Fig. 4 illustrates a section at the level of the lesion showing

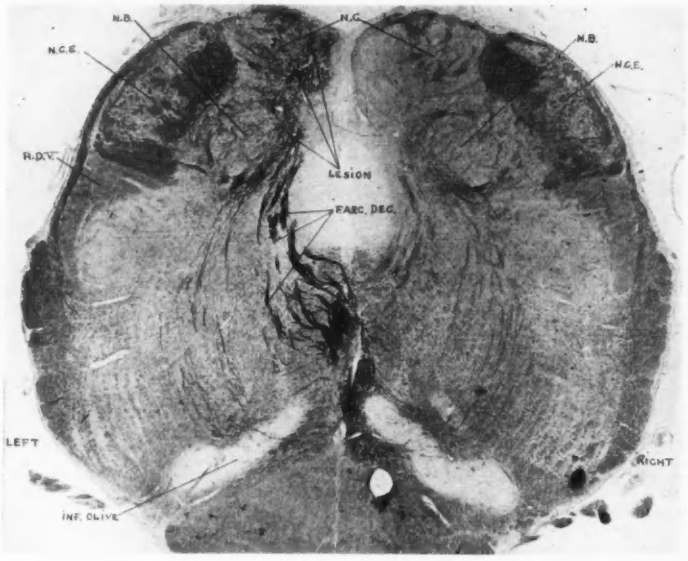

FIG. 4.—Section of the medulla from the animal described in Protocol 2, showing the point of maximum involvement of the left nucleus gracilis. The lesion encroaches slightly on the dorso-medial tip of the nucleus cuneatus in its caudal levels. The degenerated arcuate fibres, mostly from the nucleus gracilis, but with a few from the tip of nucleus cuneatus, can be clearly seen crossing to form the medial lemniscus. Marchi preparation. Inf. Olive, inferior olive; R.D.V., descending root of the 5th nerve; N.C.E., external cuneate nucleus; N.B., nucleus cuneatus; N.G., nucleus gracilis; F.Arc., arcuate fibres; Deg. (after initials), degenerated.

the destruction of the nucleus gracilis, and slight involvement of the most caudal and medial portion of the nucleus cuneatus. A few of the most dorso-medial fibres of the funiculus cuneatus were also injured as they passed the dorso-lateral border of the nucleus gracilis at its caudal extremity. This accounts for the few granules of degeneration in the nucleus cuneatus and in the external cuneate nucleus or Clarke-Monakow's nucleus. The degeneration

from the lesion of the nucleus gracilis could be followed frontally through the most medial of the internal arcuate fibres into the interolivary space and into the medial lemniscus. At the level of its greatest development the nucleus cuneatus is entirely free from damage. Fig. 5 shows the ascending degeneration in the medial lemniscus at a higher level. At lower levels the spinal cord contained no pyramidal degeneration.

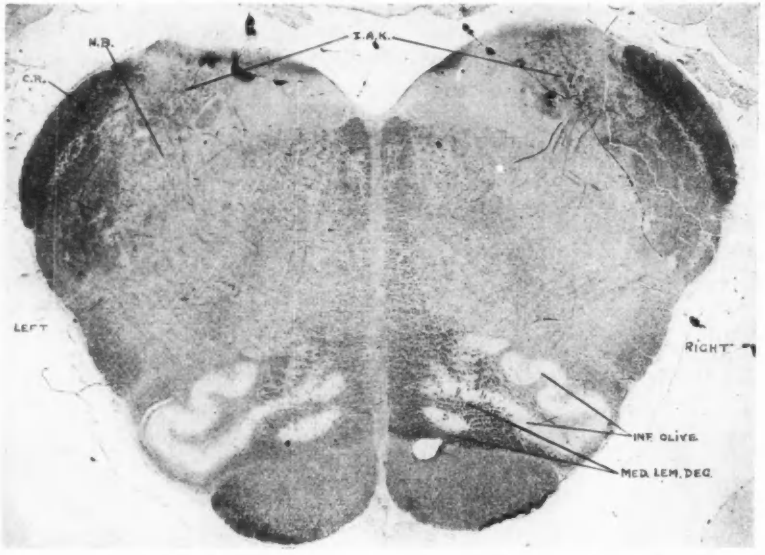

FIG. 5.—Section of the medulla from the same case as fig. 4 but at a higher level showing absence of involvement of the left nucleus cuneatus. The degeneration in the right medial lemniscus can be clearly seen. Marchi preparation. C.R., corpus restiforme; N.B., nucleus cuneatus; I.A.K., juxtarestiform bodies; Inf. Olive, inferior olive; Med. Lem., medial lemniscus; Deg. (after initials), degenerated.

Summary: A lesion limited to one nucleus gracilis was associated with symptoms confined practically entirely to the ipsilateral hind-limb. The slight temporary involvement of the arm may have resulted from slight injury of the most caudal portion of the nucleus cuneatus.

Protocol No. 3—*Cer.* 40.

Operation, January 25, 1934: *Lesion of the right nucleus cuneatus.*—While the animal was coming out of the anæsthetic there was a slight asymmetry owing to a flexion of the right fore-limb, but this disappeared rapidly as the anæsthesia wore off.

Three hours after operation.—With the animal well out of the anæsthetic

there is very definite right-sided impairment, especially in the fore-limb. On movement the animal stumbles towards the right. It sits with the right side against the cage. There are no forced swaying movements such as are seen in vestibular animals. While sitting still the right fore-limb is slightly flexed at the elbow, the hand is in a normal position or slightly extended, and the arm is adducted. The right hand is not used in reaching for food, but the animal does this readily and accurately with the left arm. When the animal is teased with a stick it makes no attempt to grasp it with the right fore-limb. Reaching and grasping are performed quite well with the hind-limb. The right arm is used only slightly and in a clumsy manner for defence. The left arm is used normally. When the animal is taken out of the cage there is a slight abduction of the right hind-foot. In walking it relies little on the right fore-limb, and the hand is often placed with the dorsum downward and little attempt is made to correct this abnormal posture. The upper arm occasionally slips sideways when weight is placed upon it. The hand is generally carried as if it were an extra appendage. The right hand is occasionally clumsy, but it is not marked. Climbing is done chiefly with three limbs and the right hind-limb seems capable of grasping the cage fairly well. The right fore-limb makes poor attempts at grasping the cage and this limb is not employed in any finely co-ordinated movements. When the animal is suspended under a horizontal bar it climbs along fairly well, using the right hind-limb to some extent and seemingly capable of holding on to the bar with it, but the right fore-limb is used apparently only for support, the upper arm being turned around the bar. There is no abnormality in any of the cranial nerves. Muscles tone is definitely diminished in the right fore-limb at the shoulder, elbow and wrist. There is also slight diminution in tone in the right hind-limb as compared to the left, but this is not very marked, and is not so severe as in animals with lesions of the nucleus gracilis. So far as can be determined there is no diminution in the animal's responses to touch, deep pressure and pin-prick in any of the limbs, trunk or head. When blindfolded the animal allows a considerable change in position to be passively impressed on the right fore-limb without manifesting any resistance, in contrast to the left arm where strenuous resistance is shown to any change in posture. Movement of the right hind-limb elicits a quick defensive response. The deep reflexes in the upper arms and the knee-jerks are active and equal on the two sides. When the animal is dropped head first, there is slight extension of the right arm but not so marked as on the normal left side. The righting, position and other labyrinthine reflexes appear normal throughout. There is, however, a definite diminution in the placing and hopping reflexes in the right fore-limb. This is not so marked in the hind-limb.

January 26: *Twenty-four hours after the operation.*—The picture is essentially the same as on the previous day. However, the animal does not stumble in running as it did then, and the involvement of the hind-limb has cleared up considerably. The symptoms are mainly confined to the right fore-limb.

January 27: *Forty-eight hours after the operation.*—The condition was unchanged.

February 1: *One week after operation.*—The disturbances are confined to to the right fore-limb; they consist in lack of spontaneous use in grasping, diminution in appreciation of the sense of position, hypotonia, over-active deep reflexes and retained superficial sensory responses. The right hind-limb appears to be slightly involved, as it is clumsy in co-ordinated movements as in climbing along underneath a bar. A good grip is present and no diminution in tone is elicited in this limb. The right fore-limb is used occasionally in active

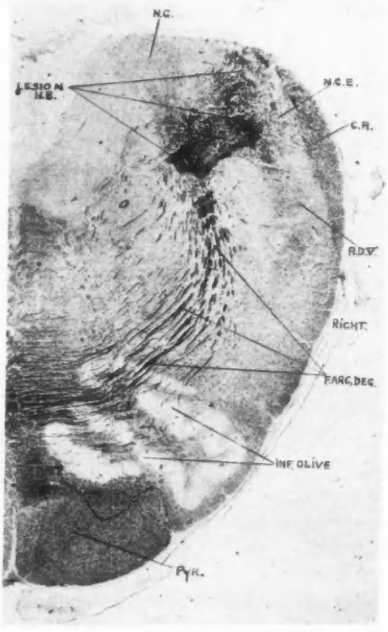

FIG. 6.—Section of the medulla from the animal described in Protocol No. 3 near the point of maximum involvement of the nucleus cuneatus. It shows involvement of the whole nucleus together with a small portion of the external cuneate nucleus (nucleus of Clarke-Monakow). The degenerated arcuate fibres from the right nucleus cuneatus can be seen bending ventrally to cross the midline to form the medial lemniscus of the opposite side. The restiform body is free from lesion. Marchi preparation. Pyr., pyramid; Inf. Olive, inferior olive: F. Arc., arcuate fibres; R.D.V., descending root of the 5th nerve; C.R., corpus restiforme; N.C.E., external cuneate nucleus; N.G., nucleus gracilis; N.B., nucleus cuneatus; Deg. (after initials), degenerated.

movements, but in feeding it acts merely as a support, and is not employed in finer movements as grasping food. During the week the various vestibular tests have been found normal. The animal shows no abnormality in swimming.

February 8: *Fourteen days after operation.*—The animal still presents

essentially the same symptoms as were described in the previous week. It was killed on this date for study in serial Marchi preparations.

Anatomical Report.—The lesion was confined to the right side and involved essentially the nucleus cuneatus proper. It extended to the cephalic end of the funiculus cuneatus, where it involved part of the funiculus itself and the most caudal portion of the external cuneate nucleus (nucleus of Clarke-Monakow). At a slightly higher level the destruction involved mainly the nucleus cuneatus. There was, however, an injury of the most lateral fibres leaving the nucleus gracilis, and the lesion encroached laterally on the most dorso-medial portion of the external cuneate nucleus (Clarke-Monakow's nucleus) (fig. 6). At a slightly higher level the lesion was confined to the

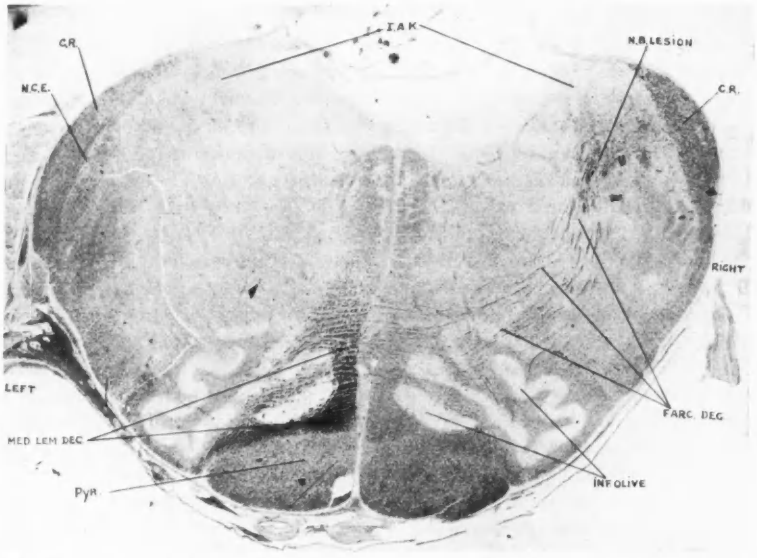

FIG. 7.—Section of the medulla from the same case as fig. 6, but near the upper end of the nucleus cuneatus which is alone involved. The degeneration in the left medial lemniscus and a few degenerated fibres in the right restiform body can be clearly seen. Marchi preparations. Pyr., Pyramid; Med. Lem., medial lemniscus; N.C.E., external cuneate nucleus; C.R., corpus restiforme; I.A.K., juxtarestiform bodies; N.B., nucleus cuneatus: F. Arc., arcuate fibres; Inf. Olive, inferior olive; Deg. (after initials), degenerated.

nucleus cuneatus. The degeneration of the arcuate fibres from the nucleus could be well seen. At a still higher level only the nucleus cuneatus was involved (fig. 7). This figure also shows the extensive degeneration in the opposite lemniscus. The restiform body on the side of the lesion contained a number of degenerated fibres, probably owing to the involvement of Clarke-Monakow's nucleus in the lower levels of the lesion. There was no evidence of injury of either the vestibular or of the pyramidal systems at any level.

To summarize, we have a monkey with a lesion involving practically all of the right nucleus cuneatus in addition to a small proportion of the efferent fibres from the nucleus gracilis. Part of Clarke-Monakow's nucleus has also been injured. Some fibres of the funiculus cuneatus have undoubtedly been cut as they pass to through or around the nucleus cuneatus to the nucleus of Clarke-Monakow. Avoidance of this complication appears to be practically impossible owing to the anatomical relationships.

Protocol No. 4, *Cer.* 122.

Operation, September 13, 1933: *Bilateral lesions of both nuclei graciles and cuneati.* When the animal came out of the anæsthetic there was marked flaccidity of all limbs.

Three hours after operation.—With the animal well out of the anæsthetic a marked disability, such as is seen following complete cervical section of the dorsum columns, is present, with the difference however that the symptoms are more marked on the right side. The main symptom is failure to use the limbs for active grasping. For example, if one approaches the cage with a small stick the animal makes violent attempts to get away, but does not reach for the stick in defence except with the left fore-limb, with which it makes some movements but fails to grasp the stick accurately; it appears to be unable to flex the hands around the stick. The right limbs make no attempt at reaching. As the animal sits in the corner of the cage the arms are adducted to the side, the elbows are flexed, and the hands dangle apparently uselessly; the hind-limbs, and particularly the right, are abducted. Although very weak, when it is allowed to leave the cage the animal attempts to walk, but its feet tend to slip on the floor, all their movements are poorly co-ordinated, the feet are flung excessively upwards and outwards, and it occasionally falls to either side, or after a few steps it may lie down on the floor. There is no oscillation of its head, which is held straight. When it reaches a cage it attempts unsuccessfully to jump. It stretches towards a support with both hands, but the left hand alone seems capable of grasping; even then it lets go quickly and the animal is therefore unable to climb. When blindfolded the animal shows no active response to passive changing of the position of the limbs, except perhaps of the left fore-limb. The muscle tone is definitely diminished in all of the limbs, but more so in the right. The deep reflexes are over-active on both sides. The cranial nerves appear normal. The animal appreciates pin-prick, touch and deep pressure, as does the normal monkey. The placing and hopping reflexes are absent, except perhaps in the left fore-limb, where there is an occasional response. The animal can right itself from either side, and if dropped head first shows a slight extension of the fore-limbs, especially of the right.

September 14: *Twenty-four hours after operation.*—The same marked inability to use the limbs in co-ordinated spontaneous grasping movements is still present. It is absolutely unable to climb and to grasp the cage except

occasionally with one or two fingers of the left fore-limb. Despite its inability to grasp the animal may, if hung from a high bar and dropped suddenly, grip the bar with both hands and hang securely for a period of fifteen to twenty seconds. The right side always relaxes first, however. The muscle tone, the deep reflexes and the special reflexes are unchanged. The disability in the hands is shown particularly when the animal attempts to eat; the right limbs are not employed, but the left hand may try, though without success, to pick up a peanut or a banana. The fingers are used clumsily and the grip is so insecure and poorly executed that the object is often dropped before it reaches the mouth. The lack of awareness of change of position in the limbs is unchanged. If the animal is placed across a bar or some support so that the arms hang free on one side and the feet on the other, it struggles to get off, but does not seem to be able to use the arms or feet to grasp the bar and lift itself from it. The sensory responses are unchanged. The gait still shows the marked excessive movements in the limbs, a rather wide base, slipping of the limbs, more particularly on the right, and the assumption of abnormal postures. When the animal sits its hind feet present a very broad base. Vestibular testing shows normal responses on both sides.

September 21: *One week after operation.*—The general physical condition of the animal is excellent. He presents, however, the same essential neurological findings as were present at the three-hour stage. During this week the animal has adopted a hopping type of gait such as was seen in our animal with cervical section of the dorsal columns, though the front limbs are used to a slightly greater extent than in the animals with the spinal lesion. There is still a lack of spontaneous grasping and inability to climb, to use the limbs in actual grasping, for defence, to bring food to the mouth, and to free it if it is placed across a bar. When the animal jumps it shows a very poor spring; there is apparently very little elasticity in the limbs, it lands heavily and the limbs slide on the floor. The sensory responses are normal throughout. The animal swims normally, and tests reveal no evidence of involvement of the vestibular apparatus.

September 24: *Eleven days after operation.*—The animal is in essentially the same state as at the earlier stage, although the symptoms are less pronounced. The chief abnormalities, including the staggering, the uncertain and inaccurate gait, the diminution in the spontaneous grasping, the hypotonia, the active deep reflexes and the loss of sense of position, are unchanged. These are more marked on the right side. The animal was killed on this date for examination by Marchi's method.

Anatomical report.—The lesion involves both nuclei graciles in their entire extent, and at its upper level it involves the whole right nucleus cuneatus. On the left a small part of the superior and outer part of this nucleus remains intact. On the left the external cuneate nucleus (nucleus of Clarke-Monakow) has been directly injured in its most dorsal quarter only. There are a few degenerated fibres in this nucleus due to involvement of the funiculus cuneatus before it enters the nucleus. On the right side the lesion extends directly into

the external cuneatus nucleus (nucleus of Clarke-Monakow) in about its upper third. The internal arcuate fibres are completely degenerated on the right, but some of those from the uninjured upper and outer portion of the left nucleus cuneatus remain unaffected. The lesion itself has not involved the fibres of the I.A.K. or the restiform body on either side. At higher levels the degenerated arcuate fibres can be followed into the medial lemniscus, in which there is symmetrical degeneration on both sides. There is no evidence of degeneration of the vestibular tracts. Both restiform bodies contain degenerated fibres,

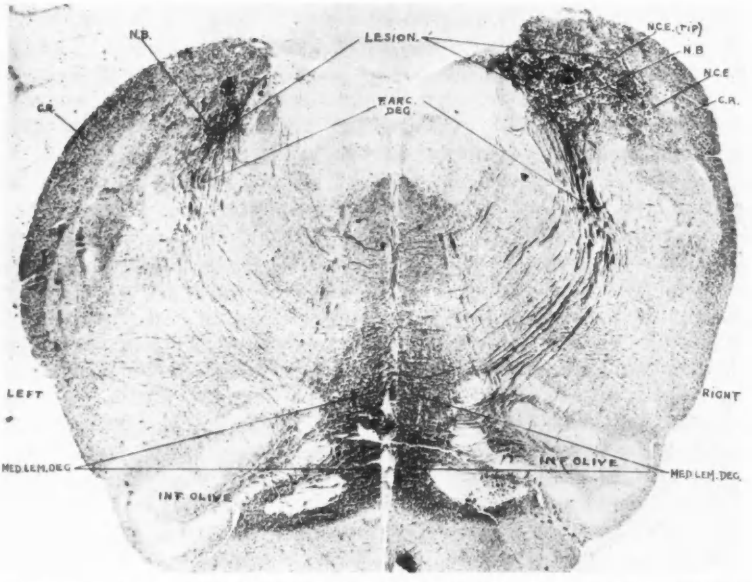

FIG. 8.—Section of the medulla from the animal described in Protocol No. 4, showing involvement of both nuclei cuneati and some involvement of the external cuneate nucleus, particularly on the right. The lesion in the nucleus cuneatus is slightly greater on the right than on the left. The degenerated arcuate fibres and the bilaterally degenerated medial lemnisci can be clearly seen at this level. Marchi preparation. Med. Lem., medial lemniscus; C.R., corpus restiforme; N.B., nucleus cuneatus; F. Arc., arcuate fibres; Inf. Olive, inferior olive; N.C.E., external cuneate nucleus; Deg. (after initials), degenerated.

which are more numerous on the right side. They presumably result from the involvement of the external cuneate nuclei, since no direct damage to the restiform body is evident. Sections below the lesion in the cervical, thoracic and lumbar segments show no degeneration in the pyramidal tracts. Fig. 8 illustrates the involvement of the higher portions of the nuclei graciles and cuneati and the resulting degeneration of internal arcuate fibres. On the right, the lesion is seen to be of greater extent, involving part of the nucleus of Clarke-Monakow. Fig. 9, at a higher level, shows the full extent of the degeneration in the medial lemniscus of each side.

In this animal the lesion involved the nuclei graciles and cuneati of both sides, but was larger on the right. On this side it extended into the external cuneate nucleus. There is degeneration of the medial lemniscus of both sides and a slight degeneration in the restiform bodies, especially on the right.

These four protocols are samples of typical cases from our large series of monkeys with different lesions of the dorsal column nuclei. In all cases the degeneration, especially when studied with the Marchi method, could be followed as far as the thalamic nuclei.

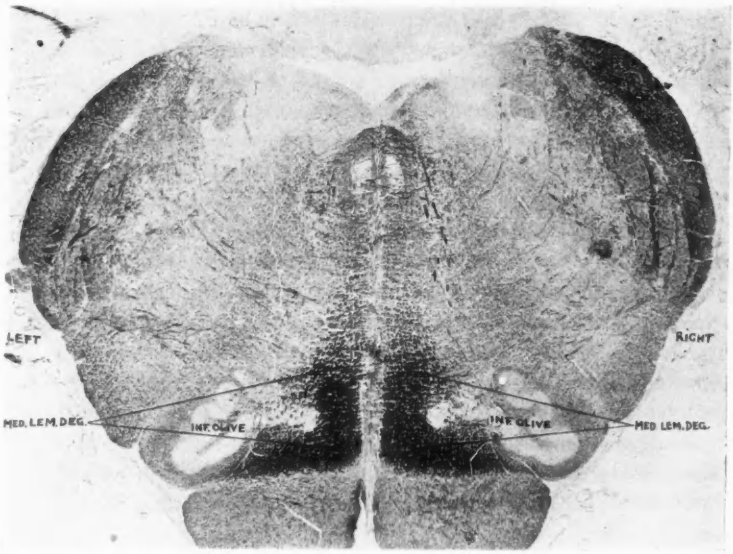

FIG. 9.—Section of the medulla from the same case as fig. 8, but at a higher level showing the bilateral symmetrical degeneration in the medial lemnisci. Marchi preparation. Med. Lem., medial lemniscus; Inf. Olive, inferior olive; Deg. (after initials), degenerated.

IV.—DISCUSSION.

In all of our animals with lesions of the dorsal column nuclei we were impressed by the similarity between their symptoms and those associated with lesions of the dorsal columns [1]. This is, of course, what one would expect, since the nuclei graciles and cuneati are the nuclei of the dorsal columns.

Zeehandelaar [10] concluded, as a result of his studies on the comparative anatomy of the dorsal column nuclei, that these nuclei are developed especially in higher animals, and that this development bears,

in the main, a direct relationship to the increasingly independent use of the upper and lower limbs and the establishment of more cortical or conscious control. According to him the dorsal column nuclei are the intermediate stations for the long dorsal column fibres carrying impulses from the limbs, the impulses from the lower limb going to the nucleus gracilis, and those from the upper to the nucleus cuneatus, from which they pass by way of the medial lemniscus to the thalamus for redistribution to the cortex. He believes that there is probably a considerable mixing and redistribution of the fibres within the dorsal column nuclei. The external cuneate nucleus, or nucleus of Clarke-Monakow, according to this author, is related to the muscles of the neck.

Our work confirms the definite projection of the fibres from the lower limbs into the nucleus gracilis, and of the fibres from the upper limbs into the internal and external portions of the nucleus cuneatus. Since lesions of either of these nuclei produce symptoms in either the hind- or the fore-leg of the same side only, the distribution appears to be entirely ipsilateral.

In unilateral lesions of the nucleus gracilis the symptoms are confined to the ipsilateral hind leg, and consist mainly of inability to control the accurate placing of the limb and a diminution in the sense of position, associated with a certain degree of hypotonia and retention of the deep reflexes. The disturbances in the hind-limb are usually not so marked when the nucleus cuneatus is destroyed. This is due to the facts by which we have explained the severer symptoms in the fore-limb as a result of the section of the funiculus cuneatus. Our experiments on the dorsal columns and on the cerebellum have tended to show that the nucleus of Clarke-Monakow, or the external cuneate nucleus, receives a large number of fibres from the funiculus cuneatus and that it sends fibres to the cerebellum by way of the restiform body of the same side. This nucleus, therefore, forms an intermediate station between fibres of the funiculus cuneatus and the cerebellum ; it receives many of the impulses from the upper limb and neck muscles which ultimately go to the cerebellum. The medial cuneate nucleus or, as we choose to call it, the nucleus cuneatus proper, on the other hand, receives fibres from the funiculus cuneatus, and in turn sends arcuate fibres to the medial lemniscus and thalamus, carrying impulses which ultimately will be associated with conscious deep sensibility. We believe, as a result of our anatomical study of lesions in the funiculus gracilis [11], that the fibres from the lower extremities terminate in the nucleus gracilis, which sends its efferent fibres into the lemniscus. A lesion of the

nucleus gracilis, therefore, involves no appreciable cerebellar connexion of the hind leg, and the disability resulting is dependent practically entirely upon a loss of the medullo-thalamic component. On the other hand, in lesions of the nucleus cuneatus, especially when the lesions extend far enough laterally to involve the nucleus of Clarke-Monakow directly, or the fibres from the funiculus cuneatus which pass into this nucleus, symptoms result not only from involvement of the fibres going to the contralateral cerebral cortex, but are also from loss of the impulses going to the ipsilateral cerebellum. The loss is noticeably greater when this is the case. This difference is exemplified very well in our Protocol No. 4, where the lesion on the right involved a greater portion of the external cuneate nucleus than it did on the left.

Our previous work [11] tended to show that there is a topographical projection from the funiculus cuneatus in Clarke-Monakow's nucleus. Its ventral end receives fibres from the upper two or three cervical segments, whereas its dorsal portion receives fibres from the lower cervical segments. It follows that a lesion extending into the ventral portion of Clarke-Monakow's nucleus would involve fibres from the upper cervical segments ending in it. On the other hand the involvement of the dorsal position of Clarke-Monakow's nucleus would involve fibres of the funiculus cuneatus coming from the lower cervical and upper thoracic segments.

In view of these facts it is easy to understand why lesions of the nuclei graciles and cuneati extending to the external cuneate nucleus, or nucleus of Clarke-Monakow, produce more severe symptoms than those limited to the nuclei graciles and cuneati, since the medullo-cerebellar fibres from the external cuneate nucleus are injured in addition to the medullo-thalamic fibres.

It is still an open question whether or not there is a greater predominance of fibres from the nucleus cuneatus or from the nucleus gracilis in the medial lemniscus. The dorsal column-cerebral component probably plays a greater rôle in the control of movements of the upper extremity than in those of the lower, since many of the movements of the lower extremity may be carried out on a spinal basis and therefore require less cortical control, or because the movements of the upper extremity in high forms, such as man and even the monkey, are a finer type and require more cortical control for successful execution. This may be the case. In order to check this experimentally, we have produced mid-line lesions of the medial lemniscus at the level of the inter-olivary space. By this operation the fibres of the lemniscus are

divided at some distance from their nuclei of origin and surrounding structures, such as the funiculus cuneatus and the external cuneate nucleus, escape injury. We found then that the symptoms following section of the medial lemniscus were more marked in the fore-limb than in the hind-limb. This justifies the conclusion that the cerebral components are more important in the control of movements of the fore-limbs than in those of the hind-limbs.

It may be of interest here to mention the effects of removal of the post-central convolutions in animals in which there had been a previous lesion of the nuclei graciles and cuneati. In another paper, dealing with the effects of lesions of the post-central convolutions [12], we report symptoms which resemble very closely those seen following lesions of the dorsal column nuclei. These are essentially a marked difficulty in performing co-ordinated movements with the limbs, associated with a deficiency in the sense of position. The symptoms here also were greater in the fore- than in the hind-legs. In one of our animals in which the gracile and cuneate nuclei had been destroyed on one side, the contralateral post-central convolution was removed after the animal had reached the chronic stage, when further improvement had ceased. In this animal the subsequent removal of the post-central contralateral convolution added nothing to the symptoms. In another animal in which both nuclei graciles and cuneati had been removed and in which the animal had likewise reached a chronic stage, subsequent removal of both post-central convolutions lead to a temporary return of the symptoms which had been observed immediately after the first operation.

It is probable that the lesions in many of our animals were more strictly confined to the dorsal column nuclei than in some of the experiments reported by various authors; this may account for our failure to obtain symptoms described by them. For example, our animals had no degeneration in the pyramidal tracts and no direct involvement of the spino-cerebellar system or restiform body. We have not observed the retropulsion or forced falling to one side which were described by Bechterew and by Ferrier and Turner. Bechterew concluded that the main symptom was a disturbance in equilibrium, but if by this something akin to a vestibular disturbance of equilibrium is meant, it cannot have been due to lesions of the dorsal column nuclei, for our animals in which there was no evidence of vestibular damage showed no tendency to rolling or forced lateropulsion.

Our findings tend to confirm our observations on monkeys with

section of the dorsal column where no evidence of loss of sensibility to pain, touch or deep pressure was found. They also confirm the exaggeration of the deep reflexes and of hypotonia after lesions of the dorsal columns. The hypotonia is not entirely due to involvement of the medullo-thalamic fibres, although it occurs with lesions of the lemniscus and of the post-central convolution. It is, however, much greater when the cerebellar components are also injured.

As yet we have not been able to produce lesions confined to the external cuneate nucleus (nucleus of Clarke-Monakow), although in one case, where alcohol injected into this nucleus with a fine needle damaged its dorsal portion only, the symptoms resembled those of a partial lesion of the ipsilateral restiform body and they were not associated with any loss of sense of position in the ipsilateral fore-limb.

It is not our intention to insist that the entire cerebellar component from the upper limb passes to the cerebellum by way of the external cuneate nucleus, in fact our experiments show that there is a cerebellar component from the upper limb in the dorsal spino-cerebellar tract, and monkeys in which lesions confined to the dorsal spino-cerebellar tract were made at the third cervical segment presented in the fore-limb symptoms typical of damage of the ipsilateral restiform body. The pathway through Clarke-Monakow's nucleus is therefore probably only one of the existing pathways, but the large number of fibres from the cervical dorsal columns which enter the nucleus indicates that it may be a pathway of considerable importance.

V.—Conclusions.

(1) Following lesions of the nuclei graciles and cuneati in macacus rhesus monkeys the symptoms which occur are mainly a loss of sense of position in all extremities, hypotonia and a transient loss or diminution of the hopping and placing reflexes. There are no appreciable changes in superficial sensibility, and the deep reflexes are not only preserved but appear to be increased.

(2) If the lesion involves exclusively the nucleus gracilis, these symptoms are limited to both hind legs if the lesion is bilateral, and to the ipsilateral leg if the lesion is unilateral.

(3) If the lesion is restricted to the nucleus cuneatus (internal cuneate nucleus) the symptoms are limited to the upper extremities if the lesion is bilateral, or to the ipsilateral extremity if the lesion is unilateral.

(4) The disturbances in the upper extremities resulting from lesions of the nuclei cuneati are more pronounced than those in the lower extremities following lesions of the nuclei graciles. This is partly due to the fact that in producing complete destruction of the nucleus cuneatus a certain number of fibres of the posterior columns to the cerebellum via the external cuneate nucleus (Clarke-Monakow's nucleus) are generally destroyed.

(5) When the lesions of the posterior column nuclei involve also the external cuneate nucleus (Clarke-Monakow's nucleus) which represents a relay station from the posterior column of the cervical segments to the cerebellum, the symptoms are more pronounced because of the involvement of the cerebellar component.

(6) The symptoms resulting from the lesions of the nuclei graciles et cuneati are similar to those following destruction of the posterior columns at high cervical levels. The intensity of the symptoms is not, however, quite as pronounced as when the posterior columns are completely destroyed. This is due to the fact that in the lesions of the posterior columns at the cervical level their cerebellar component which passes through the external cuneate nucleus (Clarke-Monakow's nucleus) is also destroyed.

(7) The symptoms of lesions of the nuclei graciles et cuneati are similar to those which follow removal of the post-central convolutions, but the latter are less pronounced since the medial lemniscus sends impulses not only to the post-central, but also to the pre-central and parietal cortex.

BIBLIOGRAPHY.

[1] Ferraro, A., and Barrera, S. E. "The Effects of Lesions of the Posterior Columns in Macacus Rhesus Monkeys," *Brain*, 1934, **57**, 307.

[2] *Idem.* "The Effects of Lesions of the Dorsal Spino-cerebellar Tract and Corpus Restiforme in the Macacus Rhesus Monkey," *Ibid.*, 1935, **58**, 174.

[3] Bechterew, W. "Ueber die Erscheinungen welche die Durchschneidung der Hinterstränge des Rückenmarkes bei Thieren herbeifuhrt uber die Beziehungen dieser Strange zur Gleichgewichtsfunction," *Arch. f. Anat. und Physio. Physiologische Abt.*, 1890, 489.

[4] Ferrier, D., and Turner, W. A. "A Record of Experiments Illustrative of the Symptomatology and Degenerations following Lesions of the Cerebellum and its Peduncles and Related Structures in Monkeys," *Proc. Roy. Soc. of London*, 1893, **54**, 476.

[5] Mott, F. W. "Experimental Enquiry upon the Afferent Tracts of the Central Nervous System of the Monkey," *Brain*, 1895, **18**, 1.

[6] Turner, W. A. "The Results of Experimental Destruction of the Tubercle of Rolando," *Ibid.*, 1895, **18**, 231.

[7] Tschermak, A. "Ueber den centralen Verlauf der aufsteigenden Hinterstrangbahnen und deren Beziehungen zu den Bahnen im Vordenseitenstrang," *Arch. f. Anat. u. Physiol. Anatomische Abt.*, 1898, 291.

[8] PROBST, M. "Zur Anatomie und Physiologie des Kleinhirns," *Arch. f. Psychiat.*, 1902, **35**, 692.

[9] MUSSEN, A. T. "Experimental Investigations on the Cerebellum," *Brain*, 1927, **50**. 313.

[10] ZEEHANDELAAR, I. "Ontogenese und Phylogenese der Hinterstrangkerne in Verband mit der Sensibilität," *Folia neurobiologica*, 1921-22, **12**, 1.

[11] FERRARO, A., and BARRERA, S. E. "Posterior Column Fibres and Their Termination in the Posterior Column Nuclei." In press for publication in the *Journ. of Comp. Neurol.*

[12] *Idem.* "The Effects of Removal of the Post-central Convolutions in the Macacus Rhesus Monkey." In preparation.

FAMILIAL SCHILDER'S DISEASE.

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In spite of the number of valuable publications concerning Schilder's disease and especially its familial variety, many problems remain unsolved. This is clearly shown by L. Bouman [8] in his recent monograph which deals with the current pathogenetic and nosological aspects of the disease. It is hoped to contribute some points that may justify the following report of a family suffering from this condition, observed and investigated by us in the Maudsley Hospital and in the Central Pathological Laboratory.

Case 1.—F. H., boy aged 9. First seen June 4, 1928, complaining of increasing deafness of three months' duration. He had been a full-time child; delivery was normal; he walked and talked at one year; he had an epileptiform fit about the age of 2; went to school at the age of 4 and was considered to be quite bright. At the age of 6 years he had a severe attack of jaundice which lasted two weeks, during which he was said to have been seriously ill. Since then he has suffered from bilious attacks and diarrhœa. Three months ago he was noticed to be somewhat deaf. This was attributed to a fall from a swing, his head having caught something in the fall. Thereafter he became dull and inattentive at school and was considered lazy. His deafness has varied, at times it was complete.

On examination he was rather apathetic, but otherwise his behaviour was normal. Vision was impaired, the pupils reacted sluggishly to light and on accommodation, the fundi were normal. There was marked deafness, and ataxia and inco-ordination of his left arm and left leg. The reflexes of arms were sluggish, those of legs were brisk. The abdominal reflexes were active and equal—the plantar reflexes were both flexor. Six months later he was more apathetic, irritable, at times noisy, screaming loudly and whining. Deafness was practically complete and visual impairment more marked. There was pallor of the optic discs, but not sufficient to account for degree of visual impairment. The ataxia was greater and he had developed a marked cerebellar posture. The deep reflexes of the arms were sluggish, those of the legs were brisk. The abdominal reflexes remained active, but both plantars were extensor in type. Wassermann reaction was negative in blood and cerobrospinal fluid. The latter contained cells 4 per c.mm.; protein 80 mg. per cent., and gave a Lange curve 5554432100 (repeated and confirmed).

The illness ran a protracted course; by June, 1929, he was able to move in

bed from side to side but unable to raise himself. He opened his mouth when his lips were touched and could swallow without apparent difficulty. He was noisy when moved and had frequent attacks of screaming. He was completely deaf and totally blind. The pupils were dilated and inactive and both optic discs showed marked atrophy. The limbs were spastic; all the deep reflexes were exaggerated. The abdominal reflexes were absent and both plantars were extensor in type. He went downhill gradually, swallowing became increasingly difficult and he died on July 15, 1929.

Post-mortem findings.—The body was emaciated. No marked changes were found in the visceral organs, which were small. There is no record of marked changes on macroscopic examination of the brain, which was hardened before section.

Pathological examination.—In horizontal sections the changes are seen to begin in the central portion of the white matter of the frontal lobe and to increase gradually, reaching a maximum extent in the parietal, temporal and occipital lobes. Here the white matter has completely disappeared. Within the affected area the formalin-hardened tissue is of a grey colour and of a peculiar elastic and tough rubber-like consistency. Weigert-Pal sections confirm the naked-eye appearance, and, in particular, show more or less complete demyelination in the posterior two-thirds of the white matter of both hemispheres. Except for a slight rarification, the myelin architecture of the cortex is intact throughout. The sub-cortical fibres generally, but not invariably, stand out against the demyelinated part of the white matter.

The basal ganglia are free from gross changes, whereas there is complete demyelination in the pyramidal and occipito-temporo-pontine tracts. The fronto-pontine tracts are better preserved. The destruction of the pyramidal tracts can be traced throughout the pons and medulla oblongata to the spinal cord, which, like the cerebellum, is otherwise free from change.

Within the demyelinized regions the disappearance of axis-cylinders in the Bielschowsky picture corresponds closely to that of the myelin sheaths. Only at the margin of the process, towards the unaffected part of the frontal lobe, is the preservation of axis cylinders greater than that of the myelin sheaths. Here the demyelination begins with a gradual patchy failure to take up the myelin stain, and offers no sharp line of demarcation. Throughout the affected areas of the white matter much fibrous glial proliferation is found, as shown by the Holzer stain. This proliferation is denser in the vicinity of the arcuate fibres than in the centre, where it is of a spongy structure.

Cell pictures (cresyl-violet, hæmatoxylin-eosin, Heidenhain, azocarmine, special glial stains) show that the cyto-architectonic structure of the cortex has not suffered considerably except for some glial proliferation immediately beneath the pia mater and in the deepest layer adjacent to the white matter. In the marginal part of the process, near the arcuate fibres and the normal frontal lobe, there is a considerable "wall" formation, consisting of multinucleated plump cells, large and small granular compound cells, proliferated astrocytes and microglial cells. The plump cells appear to be the earliest

sign of the process. The oligodendroglia is not appreciably affected in the demarcation zone, no mucocytic material being found. The nearer one proceeds to the centre of the process the more do granular compound cells decrease in number. The prevailing cell here is the plump cell which is found with almost monotonous regularity (fig. 1). Granular compound cells in larger quantities are confined to the vessel sheaths. Micro- and oligodendroglia are, in contrast to the marginal zone, definitely diminished in the centre of the process. There is throughout the demyelinated area a considerable amount of inflammatory reaction made up of lymphocytes and plasma cells which penetrate very frequently the glial membrane and lie free in the parenchyma. Many of the granular compound cells round the vessels contain yellowish green pigment (with cresyl-violet), giving a marked iron reaction. This is never found in the cortex. No inflammatory changes of any marked degree occur outside the affected area.

With Scharlach-R stain one is struck by the excessive amount of "neutral" fat in many of the phagocytic and endothelial cells of the marginal parts. As the centre of the process is approached, this bright red colour is encountered only in a few endothelial and granular compound cells around the vessels. Here most of the lipoid remains in the "prelipoid" stage. The plump cells, both at the margin and at the centre, either contain no fat, or show only a few brick-coloured granules in the periphery of the cell bodies and their processes. These granules are also demonstrable sometimes with iron hæmatoxylin, Bielschowsky's and azocarmine stain. In general, however, these staining methods do not reveal more of these substances than the Scharlach-R method, unlike the case recorded by van Bogaert and Scholz [7]. Many of the prelipoid inclusions resist solution after treatment for forty-eight hours in acetone, pyridine, xylol, ether, chloroform, ethylalcohol, methyl-alcohol, hydrochloric-acid-alcohol or mixtures of these fat solvents, whilst all the bright coloured substances are readily dissolved. Exposure to heat at 50° has no apparent affect on the prelipoids. The result of the histochemical treatment corresponds in some degree to that obtained by Schlesinger, Greenfield and Stern [31] in a case of late infantile amaurotic idiocy. No prelipoid substances are found in the unaffected frontal lobe.

The histological investigation of the organs is not very fruitful. There is a moderate degree of fatty degeneration in the cells of the liver and the tubules of the kidney. The spleen, pituitary, suprarenals, pancreas, thyroid, parathyroid and the lymphatic glands appear normal. The testicle is immature and contains a small well-defined tumour-like focus, consisting of epithelial cells. All the fatty substances in the organs are of the common neutral fat character and dissolve readily in the normal fat solvents. No prelipoids are encountered.

Case 2.—D. H., a boy aged 4, was brought for examination by his mother, on March 21, 1929, as she considered that he was becoming like his elder brother. He complained of severe headaches, sickness, vomiting and diarrhœa —was definitely jaundiced during the past ten days. He was unsteady on his

feet and tended to fall frequently. His left pupil was larger than the right, but they reacted normally. No other abnormal signs were made out on neurological examination. His gastro-intestinal trouble cleared up within seven days. Level of general intelligence was normal. He remained under observation. Although he was unsteady on his feet and appeared to drag his left leg no definite weakness was made out. In December 1931 he was admitted to hospital. His general condition was poor. His gait was unsteady and he threw out his legs with wide base. There were extensive septic abrasions on each knee owing to frequent falls. Romberg's sign was negative; the sense of position was good. No abnormality of sensation was detected. Speech was somewhat slurred. The pupils were unequal, but reacted normally; the fundi were normal. Hearing was not impaired. The deep reflexes of arms and legs were active, the abdominal reflexes were active, and both plantars were flexor in type. The Wassermann reaction was negative in the blood and cerebrospinal fluid. The latter contained cells 3 per c.mm., protein 15 mg. per cent.; the Lange reaction was negative. Throughout 1932 he complained of periodic attacks of severe headache accompanied by sickness and vomiting.

The following year his symptoms became rapidly more severe. In May 1933 his hearing was less acute and he had difficulty in seeing. By September considerable deterioration had developed; he was quite deaf and totally blind, the pupils were large, equal and inactive, and his optic discs showed atrophy. His speech was slurred, his talk was at times an unintelligible jargon. At other times one could make out quite easily what he said. The cerebrospinal fluid was re-examined; the Wassermann reaction was negative, the cells were 5 per c.mm., and protein 80 mg. The Lange test gave 1243210000. Three months later he was confined to bed, the condition was progressing rapidly. He sat in a characteristic pose, head held at an angle, occiput to the left and chin pointed to the right. The degree of pallor of optic discs had increased. His legs were spastic and the deep reflexes of the limbs were exaggerated. The abdominal reflexes were absent and both plantar reflexes were extensor in type. He was frequently noisy, resisted attention, feeding was difficult and he had difficulty in swallowing. He was frequently incontinent of urine. On January 5, 1934, he developed a twitching of the right side of his mouth and face which extended to eyelids and then to left arm and leg. He had continued seizures for a period of six hours, did not regain consciousness, and died the following day.

Post-mortem findings.—No gross changes were visible in the visceral organs, except a few patches of fatty change in the liver and encapsulated old tuberculous foci in the right lung. The brain weighed 1,410 grms. No macroscopic changes are on record. It was hardened before section.

Pathological examination.—After hardening in formalin coronal sections were made throughout the brain. The involvement of the white matter is strikingly similar to that of the first case in that the frontal lobe is preserved as a whole, while extending backwards the changes increase rapidly until they involve all the white matter. As in the first case, the process is nearly

symmetrical. The consistency is much softer and is of a gelatinous character. The arcuate fibres are usually well preserved. The corpus callosum is less affected than the rest of the white matter. Immediately in front of the anterior part of the process is an œdema which also involves the cortex.

Myelin sections show in general the same extent of degeneration as Case No. 1, except that here there is also a demyelination of the fronto-pontine tracts and the pyramidal tracts are involved to a minor degree. The changes in the chiasma and the optic tracts will be considered later.

As to histological detail we only mention that there is a demyelination with corresponding destruction of the axis-cylinders similar to that found in Case 1. In the affected areas the infiltration of the vessels with plasma cells and lymphocytes penetrating into the parenchyma, is still more pronounced (fig. 2). No iron is found in the cells of the vessels. In the demarcation zone, near the arcuate fibres and the frontal lobe, the degeneration of the myelin appears to be more intense than in the first case and the microglial proliferation is greater. Corresponding to the zone of œdema there is a considerable degree of swelling of the oligodendroglia, but no mucocytic material is formed. Again the first signs of the process are plump cells. Sometimes one gains the impression that the oligodendroglia participates in the formation of granular compound cells. In the centre of the process oligodendro- and micro-glia are again markedly diminished. Plump cells, so predominant a feature in the first case, are here only rarely seen. Between the much looser fibrous glial network formed by ordinary astrocytes, large masses of granular compound cells are found (fig. 2). Scharlach-R stain reveals, not only in the marginal part but also in the centre, much brighter coloured lipoidal material which can be washed out nearly completely by all the fat solvents previously mentioned. Even those lipoids showing the pink colour readily dissolve. Plump cells do not participate in the uptake of lipoids. Some of the prelipoid substances are stainable by iron hæmatoxylin and ammoniacal silver. The frontal lobe is histologically normal. The cortex shows only a slight diffuse thickening of the covering glial layer; in the deepest layers adjacent to the process, changes occur in the ganglion cells and proliferation of the glia is to be noted.

Histological examination of the visceral organs does not reveal any changes worthy of note.

Case 3.—E. H. (Mrs.), aged 37, attended hospital April 14, 1934, complaining of general weakness, loss of interest and ataxia. She dated the onset of her symptoms to four months previously, though she had been working, as a cleaner, until two weeks ago. Her previous health had been good, without history of serious illnesses. She has been married sixteen years; was unhappy, as her husband was alcoholic and frequently abused her. They separated four years ago. There had been four children by this marriage. She has had a fifth since she separated from husband who denies paternity:—

(1) Frank, died aged 10—Case 1.

(2) Edgar, aged 13. General condition not good, frequent diarrhœa, con-

PLATE I.

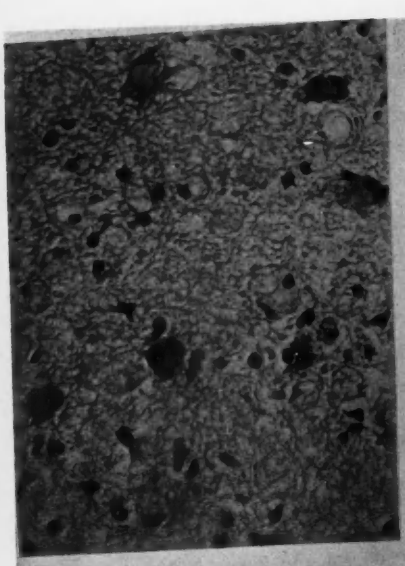


Fig. 1

Fig. 2

a

b

c

d

Fig. 4

To illustrate paper by Alfred Meyer and Thos. Tennent.

sidered to be unsteady on feet and to "fall about." Never without septic abrasions on knees and legs. Neurological examination completely negative.

(3) Stanley, aged 11. General health poor, said to have gastro-intestinal trouble, otherwise nil abnormal.

(4) Dennis, died aged 9. Case 2.

(5) Peter, aged 4, enjoys good health; is in a residential school.

Family history: It has been possible to obtain particulars of four generations of both the patient and her husband. These are tabulated in fig. 3. Chronic alcoholism is prominent on both sides. There is no history of nervous illness, nor is there any record of an illness, the course of which seemed obscure, or like that of any of the patients here recorded.

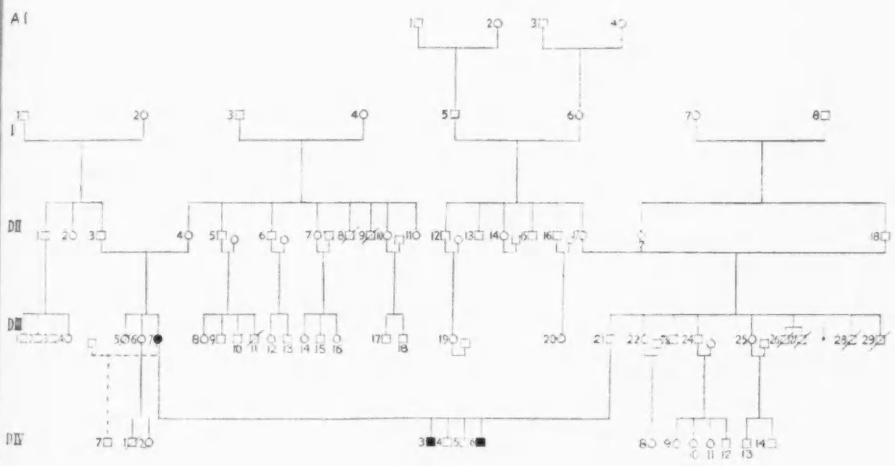


FIG. 3.

On examination she was apprehensive, emotionally unstable and convinced she was becoming like her two children who had died in hospital. She complained of mistiness of vision. Her visual acuity was R. $\frac{6}{6}$, L. $\frac{6}{9}$; there was no impairment in her visual fields. The fundi were normal. Hearing in her left ear was somewhat impaired. She complained of ataxia. With eyes closed and feet together she swayed considerably but maintained her balance. She was unable to walk along a line on the floor. Sensibility to touch and pinprick was more acute on the right side of the body. Vibration sense was lost on the left leg but present on the right. There was no astereognosis. The deep reflexes of the arms were equal and active, those of the right leg were more active than those of the left. Upper abdominal reflexes were active, the lower were absent. The left plantar reflex was extensor in type, the right gave a doubtful response. The Wassermann reaction was negative in the blood and cerebrospinal fluid. The fluid contained cells 2 c.mm., and protein

30 mg. per cent. Lange's reaction was negative. Gastric test meal shows slight diminution in acidity, well within normal limits. Blood-count: R.B.Cs. 4,520,000; W.B.Cs. 4,700; Hb. 10·4 grm. per cent.; C.I. 0·8; blood cholesterol 90 mg. per cent.

Since then her condition has progressed slowly. Giddiness troubled her and she has injured herself by falling. Headaches associated with vomiting were troublesome. She has developed incontinence of urine. There is hyperæsthesia to touch over the whole of the left side of her body. Vibration sense on the upper limbs is intact, but is lost over both lower extremities. She fails to recognize figures written on the skin of her legs but does so quite easily over her arms. The degree of ataxia has increased and Romberg's sign is positive. There is marked hyperflexion in walking. No definite paresis is present. The pupils are equal and react briskly to light and on accommodation. The temporal sides of both discs are somewhat pale; the visual fields are normal. The ocular movements are normal and there is no nystagmus. Some degree of deafness has developed in the left ear but cranial nerves are otherwise normal. The deep reflexes of upper limbs are active and appear equal; those of lower limbs are exaggerated, greater on the right leg. There is a right ankle clonus. The abdominal reflexes are absent. Both plantar reflexes are extensor in type.

The discussion can be limited with advantage to a few of the most important features.

The familial character of our cases is obvious. It is interesting to note that the mother's illness did not manifest itself before the onset of the disease in her children. A clear diagnosis of her condition is not yet possible. There are symptoms suggestive of a condition like disseminated sclerosis rather than spastic spinal paralysis. Early subacute combined degeneration has also been considered. As to the diagnostic evaluation of the condition occurring in members of earlier generations, it is well to remember that pathological evidence on this point is, as far as we can see, not yet on record.

It is striking to note the recent rapid increase in the number of familial cases since Krabbe [23], and particularly Scholz [34], drew attention to their occurrence. Since then one of Collier and Greenfield's [12] sporadic cases has proved to be familial, and the same applies, as we shall show in a later communication, to the first case of Stewart, Greenfield and Blandy [37]. It may well be that the familial group will play a much more dominant role in future classification.

From the pathological point of view the similarity in distribution is very striking in the two cases examined. It shows itself not only in the preservation of corresponding parts of the frontal lobes, but also in preservation of the basal ganglia, cerebellum, and even, as we will see

later, in minor characteristics, such as lesions of the chiasma and optic tracts. This similarity of distribution may be determined by a constitutional factor. It must be mentioned, however, that the pathological changes found in familial cases do not always correspond so clearly, as exemplified by cases in the literature and our own further observations, not yet published.

The intensity of inflammation and the presence of inflammatory cells outside the vessel sheaths seems to surpass what has been found previously in familial cases. It may still be called "symptomatic," particularly if one considers that the tendency of a secondary inflammatory response to the decomposition of myelin is greater than usual (Cheng Yü Lin) [11]. It exemplifies, however, the difficulties of a classification based on the presence or absence of inflammatory changes, which is still believed, at least in some quarters, to be valid. The deep-rooted tendency to base classification on more or less superficial single histological features, is losing more and more ground (Spielmeyer [36], Bielschowsky and Maas [3], Guttmann and Bodechtel) [4, 5]. This applies not only to inflammation, but also to Bielschowsky's and Henneberg's [2] criterion, that in the "inflammatory" group the total demyelination originates from separate coalescing foci. We have seen this form of growth in another familial case which will be described in a later communication. It may even apply to the prelipoid substances which Scholz believes to be a feature of the heredo-degenerative cases only. Perhaps they have been found prevailingly in familial cases because they have there been specially searched for. The insufficiency of a histological classification is still more obvious if one takes into account the possibility of an extracerebral pathogenic mechanism. Take the example of pernicious anæmia. Here, Strauss, Heath and Castle [38] have advanced the view that the pathological changes in the blood and in the cerebrospinal system result from the lack of a factor normally present, the disappearance of which may be caused by an intrinsic abnormal function of the liver and the mucosa of the stomach, or by an extrinsic nutritional deficiency. According to this view, whatever the difference in the origin, the final attack on the central nervous system will be the same. We do not want to associate pernicious anæmia too closely with the processes included under the heading of "Schilder's disease"; it is not inconceivable that in the latter an extracerebral factor may be originally at work. (Ferraro [15], Macnamara and Dickson [26], *et al.*).

Greenfield [19] recently had something similar in view when he suggested that his cases of infantile progressive sclerosis were supplied

with abnormal lipoids. It is in the light of such or similar conceptions that gastro-intestinal troubles at the onset of symptoms, in a group of Schilder's disease, become important. Globus [18] considers an onset with gastro-intestinal troubles as characteristic of many cases of Schilder's disease. Gastro-intestinal disturbances preceded not only the neurological symptoms of the two cases described here, but they are also recorded in the history of two of the other children, only one of whom shows as yet nervous symptoms (slight degree of ataxia). The interval between the gastro-intestinal attack and the manifestation of neurological symptoms in our two cases is very long (the mother suggests that the children never fully recovered from the attack of jaundice).

The consideration of a possible extracerebral pathogenic factor makes careful examination of the bodily organs indispensable. Moreover, the formation of prelipoid substances in cases of Schilder's disease has suggested comparison with amaurotic idiocy, which is, as shown by Bielschowsky and others, often associated with the changes in the viscera, known as Niemann-Pick disease. The appearance of prelipoid material in otherwise intact areas of the brain in cases of Schilder's disease (Bielschowsky and Henneberg) [2], the enlargement of liver and spleen in Kaltenbach's [22] case and the metachromatic substances found by Witte [40] in the visceral organs, seem to point in the direction of a more generalized disturbance. Histological examination of the viscera of familial cases of Schilder's disease has, however, been somewhat neglected. The result in our cases was negative; changes seen do not differ from those commonly found in the terminal stages of other conditions. There are no prelipoid substances comparable to those found in Niemann-Pick disease, and in xanthomatosis which might be connected also with lesions of the white matter (Davison) [13]. Unfortunately, we were not able to examine histologically the gastro-intestinal tract of our cases.

The presence of prelipoid substances has been used by Scholz [33, 34], who discovered them first, as the basis of his theory of primary glial insufficiency, which has found much favour (Bielschowsky and Henneberg [2], van Bogaert and Bertrand [6] and others). It is interesting, however, to note that our second case, with its more rapid course both clinically and pathologically, showed a greater activity of the microglia in the formation of ordinary scavenger cells than our first case, which resembles more closely that recorded by van Bogaert and Scholz [7]. Correspondingly, the breakdown of degenerated myelin to neutral fat is in the second case much more complete than in the first,

as seen, for example, from the reaction of the lipoids towards flat solvents. That is only a single observation, but in the light of other views regarding Scholz's interpretation (Bodechtel and Guttmann[4, 5], Patrassi [29], Hallervorden and Spatz [20], Bouman [8]) it may become more significant. Cases like those described by Ferraro [14], which combine a mild and protracted clinical course with extreme passivity of the glia and the most incomplete elaboration of the destroyed myelin, emphasize the difficulties of interpretation. Passivity of the glia does not necessarily mean insufficiency, and, according to Patrassi [29], the prelipoid substances can also be accounted for by a primarily abnormal character of the myelin products of disintegration.

Another group of writers suggests as the cause of the process a primary attack on the oligodendroglia (Hortega [21], Bailey and Schaltenbrand [1], Collier and Greenfield [12], Levaditi [24, 25] and others). Greenfield [19] gave recently an impressive example of mucocytic degeneration of the oligodendroglia connected with demyelination in a disease termed by him "progressive infantile sclerosis." But in Schilder's disease the reports so far available on the histological behaviour of the oligodendroglia, do not allow a general application of this finding. In our own cases we regard the changes of the oligodendroglia as secondary. Swelling of the oligodendroglia is seen only in one case, in a zone where it can be interpreted as a result of the particularly intense process of destruction. The diminution of the oligodendroglia in the centre of the process can also be considered as a secondary phenomenon, the more so as we do not know enough about its possible participation in the formation of granular compound cells.

We have not yet reported the changes found in the peripheral optic system. There was in both of our cases irregular demyelination of the chiasma, extending to the optic nerves. In coronal sections of both our cases the peripheral, and more particularly the ventral, part of the optic tract is better preserved than the central and the upper part (fig. 4, *a* and *b*). This is also seen in the third familial case not yet published (fig. 4, *c*). Occasionally the lesion is confined to the centre (fig. 4, *c*). Fat stain shows the process to be the same as that found in the cerebral white matter. At the zone of demarcation one finds a layer of fat-laden globoid cells, indicating that the lesion is proceeding from the centre towards the periphery (fig. 4, *d*). This is of pathogenic interest because Monnier and Walthard [28] described recently similar centrally placed lesions of the optic tract in a case of cerebral lues, in which the anterior choroid artery supplying a part of the optic tract was

found to be obliterated. This might suggest a vascular origin of the changes in the optic tract in cases of Schilder's disease.

There is no systematic limitation of the lesion to functional units, although it is obvious that, according to the scheme of Brouwer and Zeeman [9, 10] and others, the papillo-macular bundle must have suffered first and to the greatest degree. Equally interesting is the striking similarity of the lesions of the optic tract to those found by Scherer [30] in the well-known disease in monkeys: the lack of peripheral optic lesions in Schilder's disease was one of the reasons that Schob [32] and Spielmeyer [36] would not accept a close relationship between both these conditions. Furthermore gastro-intestinal disturbances, so outstanding a feature in Schob's and Scherer's disease in monkeys, are not foreign to Schilder's disease, as exemplified by Globus' [18] and our own cases. The same applies to "honey-combed" lesions in the spinal cord found in the monkeys, which made Scherer think of a condition related to pernicious anæmia. Honeycombed lesions occur in Schilder's disease (Wertham [39], Marinesco and co-workers) [27] and they might be found more frequently if more attention were paid to the point. There is no necessity to interpret the case described by the Roumanian authors as a combination of Schilder's disease and ophthalmo-neuromyelitis.

Histopathological similarities do not necessarily indicate a close ætiological relationship, as pointed out by Spielmeyer [35]. Moreover, since Schilder's disease is not likely to be a disease entity, findings seen in one of its groups need not apply to another. The fact, however, that an apparently epidemic and transmissible (Gaertner) [16, 17] disease and cases of Schilder's disease of heredofamilial nature have so much in common, presents an interesting pathogenic problem requiring further attention.

Summary.

The clinical and pathological records of two brothers suffering from Schilder's disease are presented. Their mother is affected by a progressive spinal condition the nature of which is still uncertain.

Gastro-intestinal troubles preceded by a long interval the nervous affection of the two brothers. These symptoms are also presented by a third brother who has slight ataxia.

There were no histological changes in the visceral organs to account for the affection of the central nervous system.

The pathogenic and ætiological views on Schilder's disease are discussed in the light of the cases investigated. Consideration is given to

the theory of primary glial affection with special regard to the difficulties of interpretation of the histological data.

The peculiar distribution of the process in the optic tract is described. It was similar to that described by Scherer in a spontaneous disease in monkeys. The nosological significance of these symptoms and of "honeycombed" patches, which are found also in Schilder's disease, is discussed as to its broader aspects.

We desire to express our thanks to Mr. C. Geary, who kindly gave us those sections he had prepared of the first case, and to Mrs. Meyer for the histological and microphotographic work in relation to both cases. We should also like to take this opportunity of expressing our thanks to Dr. Golla, Director of the Central Pathological Laboratory, and to Dr. Mapother, Medical Superintendent of the Maudsley Hospital. We wish to express our indebtedness to the Rockefeller Foundation, who gave a grant to one of us (A.M.); also to the Medical Research Council for a grant made for incidental expenses.

REFERENCES.

[1] Bailey, P., and Schaltenbrand, G. *Zeitschr. f. Nervenheilk.*, 1927, **97**, 231.
[2] Bielschowsky, M., and Henneberg, R. *Journ. f. Psychol. u. Neurol.*, 1928, **36**, 131.
[3] Bielschowsky, M., and Maas, O. *Ibid.*, 1932, **44**, 138.
[4] Bodechtel, G., and Guttmann, E. *Zeitschr. f. d. g. Psychiatr. u. Neurol.*, 1931, **133**, 601.
[5] *Idem. Ibid.*, 1932, **138**, 544.
[6] Bogaert, L. v., and Bertrand, J. *Rev. Neurol.*, 1933, **2**, 249.
[7] Bogaert, L. v., and Scholz, W. *Zeitschr. f. d. g. Neurol. u. Psychiatr.*, 1932, **141**, 510.
[8] Bouman, L. "Diffuse Sclerosis." London, 1934.
[9] Brouwer, B., and Zeeman, W. P. C. *Brain*, 1926, **49**, 1.
[10] Brouwer, B., Zeeman, W. P. C., and Houwer, A. W. H. *Schweiz. Arch. f. Neurol u. Psychiatr.*, 1923, **13**, 118.
[11] Cheng Yü Lin. *Arch. of Neurol. and Psychiatr.*, 1934, **31**, 1247.
[12] Collier, J., and Greenfield, J. G. *Brain*, 1924, **47**, 489.
[13] Davison, C. *Arch. of Neurol. and Psychiatr.*, 1933, **30**, 75.
[14] Ferraro, A. *Ibid.*, 1928, **20**, 1065.
[15] *Idem. Psychiatr. Quart.*, 1933, **7**, 267.
[16] Gaertner, W. *Klin. Wochnschr.*, 1932, **2**, 905.
[17] *Idem. Arch. f. Psychiatr. u. Nerv.*, 1933, **99**, 822.
[18] Globus, J. H. In W. Penfield: "Cytology and Cellular Pathology of the Central Nervous System." New York, 1932, **3**, 1145.
[19] Greenfield, J. G. *Proc. Roy. Soc. Med.*, 1933, **26**, 18.
[20] Hallervorden, I., and Spatz, H. *Arch. f. Psychiatr. u. Nerv.*, 1933, **98**, 641.
[21] del Rio Hortega, P. *Memorias de la Real. Soc. Esp. de Hist. Nat.*, 1928, **14**, 5.
[22] Kaltenbach, H. *Zeitschr. f. d. g. Psychiatr. u. Neurol.*, 1922, **75**, 138.
[23] Krabbe, K. *Brain*, 1916, **39**, 74.
[24] Levaditi, C. *Ann. de l'Inst. Pasteur*, 1930, **45**, 673.
[25] Levaditi, C., Lepine, P., and Schoen, R. *Compt. rend. Soc. de Biol.*, 1930, **54**, 986.
[26] Macnamara, E. D., and Dickson, W. C. *Proc. Roy. Soc. Med.*, 1933, **26**, 297.

[27] Marinesco, G., State Draganesco, Sager, O., and Grigoresco, D. *Rev. Neurol.*, 1930, **2**, 193.
[28] Monnier, M., and Walthard, K. M. *Monatschr. f. Psychiatr. u. Neurol.*, 1934, **90**, 60.
[29] Patrassi, G. *Virchow's Archiv*, 1931, **281**, 98.
[30] Scherer, H. J. *Zeitschr. f. d. g. Neurol. u. Psychiatr.*, 1932, **141**, 212.
[31] Schlesinger, B., Greenfield, J. G., and Stern, R. O. *Arch. Dis. in Childhood*, 1934, **9**, 49.
[32] Schob, F. *Zeitschr. f. d. g. Neurol. u. Psychiatr.*, 1931, **135**, 95.
[33] Scholz, W. *Monatschr. f. Psychiatr. u. Neurol.*, 1933, **86**, 111.
[34] *Idem. Zeitschr. f. d. g. Neurol. u. Psychiatr.*, 1925, **99**, 651.
[35] Spielmeyer, W. "Verhdl. deutsche Nervenaerzte." Leipzig, 1929. 86.
[36] *Idem. Zeitschr. f. Hyg. u. Infektionskrankh.*, 1931, **113**, 170.
[37] Stewart, T. G., Greenfield, J. G., and Blandy, M. A. *Brain*, 1927, **50**, 1.
[38] Strauss, M. B., Heath, C. W., and Castle, W. B. *Amer. Journ. Med. Sci.*, 1931, **182**, 741.
[39] Wertham, F. *Arch. of Neurol. and Psychiatr.*, 1932, **27**, 1380.
[40] Witte, F. *Münch. med. Wochnschr.*, 1921, **68**, 69.

THE PHYSIOLOGICAL PATHOGENESIS OF EPILEPSY.[1]

BY WILLIAM G. LENNOX, M.D.

WHEN Hippocrates made the bold prediction that whoever learned to make the epileptic humid or dry, hot or cold, could cure his disease, he had a conception, the essential rightness of which the medical world is only now appreciating. We now know that certain alterations of the physiology of the body, though they do not cure epilepsy, may modify the frequency or force of epileptic seizures. Induction of alkalosis by means of hyperpnœa, or by the ingestion of large amounts of alkali, tends to precipitate seizures. Acidosis (induced by starvation, by ingestion of a ketogenic diet or of acids or acid-forming salts, by breathing of air rich in carbon dioxide, or by increasing the concentration of the lactic acid of the blood through muscular work) tends to decrease seizures in certain individuals having very frequent attacks. Again, the retention of fluids by the body, secured by the injection of pitressin with simultaneous ingestion of large amounts of water, may precipitate convulsions, whereas a severe limitation of the fluid intake inhibits them. These matters have received consideration in previous publications and will not be dealt with now. I shall attempt only to review recent studies from our own laboratories which deal with the rôle in epilepsy of the cerebral circulation and of oxygen metabolism.

The question must first be answered, "Is there evidence of a specific defect in the cerebral circulation or in the oxygen metabolism of epileptics?" Spasm of the arterioles of the brain with resulting generalized cerebral anæmia has been a favourite theory in explanation of the sudden onset of seizures. The theory is excellent; the experimental proof a failure. Dr. and Mrs. Gibbs and I [1] have recorded the flow of blood through the brains of patients by means of a thermoelectric flow recorder inserted into an internal jugular vein. Records were secured of ten patients having either spontaneous or induced fits. There was no decrease in the blood flow immediately before a spontaneous seizure. We believe that the theory of a generalized cerebral

[1] Read before the International Neurological Congress in London on July 28, 1935. This is No. XX in a series entitled "Studies in Epilepsy," aided by a grant from the Harvard Epilepsy Commission.

anæmia as a cause of spontaneous seizures should be placed reverently in the museum of outmoded medical theories. The possibility of a spasm of a single vessel with a resulting localized area of anæmia remains. Two bits of evidence are against: following the constriction of single cortical vessels frequently observed *by* neurosurgeons, muscle spasm or paralysis does not ordinarily ensue; and the induction of generalized cerebral anæmia (with consequent local anæmia) is not a certain method of precipitating a seizure in the ordinary epileptic. However, this question of localized vascular spasm requires more study.

A continuous and sufficient supply of oxygen is essential for the proper functioning of nervous tissues. Denial of oxygen to the brain for a few seconds results in unconsciousness and tonic muscle spasm. We determined, therefore, to submit the relationship of oxygen and seizures to careful study.

Is the total volume of oxygen consumed by patients normal? Between seizures the oxygen consumption is normal or only slightly reduced. Of more significance is the fact that immediately before and during non-convulsive seizures there is no alteration in the total oxygen consumption of the body. I have numerous records of *petit mal* seizures which have occurred while patients were attached to a metabolism machine for measuring oxygen consumption. Portions of the breathing records of four patients are shown in fig. 1. In none does the occurrence of a seizure significantly influence the smooth upward slope of the curve which indicates the volume of oxygen consumed.

Is the oxygen tension of the circulating blood normal? Mrs. Gibbs and I have measured the oxygen content of the blood of a large group of patients, taking blood from an artery, and also from an internal jugular and from a basilic or femoral vein. The arterial blood is of first importance in examination, for a gross defect in the tension of oxygen going to the brain would be of obvious significance. We measured tne oxygen saturation of the arterial blood of eighty-eight patients. In only 54 per cent. was the saturation within the range commonly accepted as normal; namely, between 94 and 99 per cent. The deficiency was, however, small. Only 11 per cent. of the bloods were less than 90 per cent. saturated. Furthermore, this defect was not confined to epileptics. Fifty-eight non-epileptic patients of the neurological ward were examined and an even smaller proportion, 46 per cent., had a normal oxygen saturation. We found that if patients with a deficient saturation were made to breathe oxygen or even to respire deeply, the saturation became normal. The difficulty,

therefore, is due to an insufficient pulmonary ventilation, the consequence of poor posture, and poor physique [2].

The venous blood from the arm was examined in one hundred instances. The average oxygen saturation (65 per cent.) is definitely lower than the normal (72 per cent.) which is the average figure culled from the literature. These findings point to a slow flow of blood through the extremities of these patients.

Is there also an abnormally low oxygen tension of the blood leaving the brain? In an effort to secure conclusive evidence on this vital point, we measured the oxygen content of blood from the internal jugular vein in 130 instances. The average oxygen saturation of 63 per cent. was even less than the saturation of blood from the arm. However, we found that patients without epilepsy or cerebral disease had an equally low saturation. Furthermore, blood drawn from an internal jugular vein during a mild seizure or during status epilepticus was found to have an oxygen saturation within normal limits [3].

The hypoxæmia of arterial and of arm vein blood encountered in a large proportion of epileptics is an expression of the stagnant physical and mental state which so often accompanies epilepsy. The hypoxæmia when present requires correction, but it cannot be a fundamental factor in the causation of seizures.

We have failed to find evidence of a defect in the supply of blood or of oxygen to the brain of epileptics. The next question is whether the frequency of seizures will be changed if the blood or oxygen supply is artificially altered. Eight years ago [4, 5], I reported that *petit mal* seizures could be induced in patients having very frequent *petit mal* if they breathed air poor in oxygen, but not so poor as to produce unconsciousness in the normal person. I have now encountered thirteen of these patients whose *petit mal* attacks could always be induced by means of an artificially induced anoxæmia. I emphasize that these were patients having from ten to several hundred *petit mal* daily. In patients with only occasional *petit* or *grand mal*, attacks are not easily induced. We produced complete unconsciousness by having patients breathe nitrogen or by causing them to faint. Syncope was induced by giving the patient sodium nitrite and then, with the aid of a tipping table, standing him erect. Of twenty *grand mal* patients rendered unconscious by cerebral anæmia or anoxæmia, only one experienced his usual convulsion. Presumably *petit mal* is more readily induced than *grand mal* because of greater frequency and lower threshold, and not because of a different intrinsic mechanism, though further study may alter this view.

In order to test the effect of the opposite condition, an over-abundance of oxygen, Dr. Behnke and I placed three patients having very frequent *petit mal* in a pressure chamber under from one to four atmospheres of absolute pressure. In the chamber the number of spontaneous seizures was 55 per cent. of the patient's usual number. Previous observations with these patients had shown that seizures in each could be regularly induced by a certain period of over-ventilation.

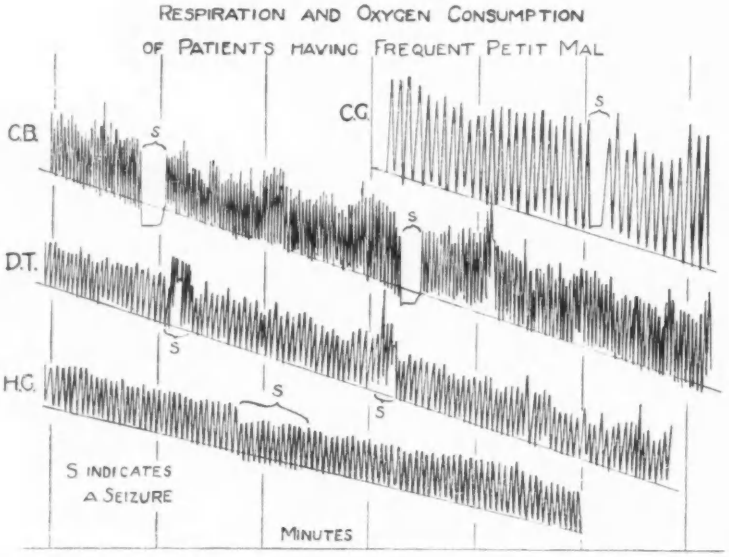


FIG. 1.—Graphic record of the oxygen consumption of four patients, as indicated by their initials. The patient was attached to a machine for measuring the basal metabolism. The records read from right to left. The upward slope of the base line indicates the volume of oxygen consumed. The excursions of the pen record the frequency and depth of respirations. The period occupied by a seizure is indicated by the letter S. There is no significant alteration in the oxygen consumption either before or during seizures.

While patients were in the chamber under pressure they performed hyperpnœa in an atmosphere of oxygen, and by this means a tension of oxygen twenty times the usual atmospheric tension was obtainable. It was found that with progressive increase in the tension of oxygen, there was progressive increase in the amount of over-ventilation required to produce a seizure. With an oxygen tension twenty times normal, five times the usual amount of over-ventilation was required [6].

These observations demonstrate that acute decrease in blood or

oxygen supply to the brain may precipitate, and acute increase in the oxygen supply may inhibit a patient's seizures.

The epileptic seizure has been compared to a reservoir impounded by a dam [7]. The springs which give rise to the imprisoned water (viz. heredity, abnormalities of the brain or of the body, disturbances of the sympathetic nervous system and of the emotions) are the fundamental causes of the attacks. A seizure, represented by an overflow of the dam, can result either from an increase in the height of the waters, or from a decrease in the height of the dam. I believe the physiological changes which we have been discussing are not the waters within, but the bank without; they act by altering seizure threshold. Obviously, raising the banks may be of only slight or temporary advantage to the patient.

These various approaches to the ætiology of epilepsy lead to a question which has been a closed door before which clinicians and investigators have come to a stand. What takes place in the brain when a seizure occurs? Thanks principally to Berger, we no longer have to depend on the circumstantial evidence of sensation or of muscle contraction. As through a door unexpectedly opened, we can perceive what is taking place within the brain. We can discard figures of speech and speak plainly of the electrical activity of the brain, and can make graphic record of this activity.

Dr. Frederic Gibbs, Dr. Hallowell Davis and I, working in the Department of Physiology of Harvard Medical School, have obtained records of the electrical potentials from the brains of twenty-one patients during hundreds of seizures. The methods and apparatus used and the observations made are presented elsewhere in detail which is impossible here [8].

In the case of *grand mal*, for a variable period before the convulsion there is an increase in the electrical activity of the brain; during the convulsion waves are slower and of very large potential; and in the period of stupor following the convulsion, there is almost complete absence of electrical activity.

Because impairment of consciousness is the essential feature of a seizure and because the muscular movements of a convulsion add complications to the record, I shall speak from now on only of *petit mal*. *Petit mal* are invariably accompanied by a burst of action potentials much larger and less frequent than the patient's usual potentials. From a frequency of 10 to 20 a second they slow to 1 to 3 a second, and from a voltage of 10 to 50 millivolts they increase to 100 to 300 millivolts.

These waves definitely represent potentials set up by discharging cells in the brain, and not the potentials of contracting muscles in the scalp or in cerebral arteries. During *petit mal* any slight twitching move-

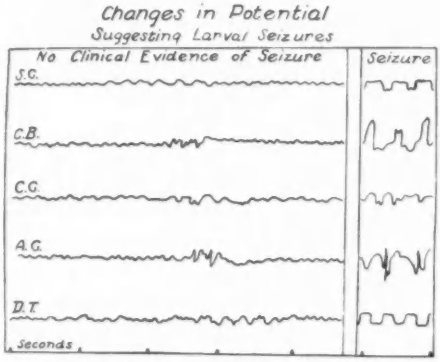


FIG. 2.—Electro-encephalograms of five patients when having *petit mal* (right hand portion) and when free of symptoms (left hand portion). The small alterations in potential during symptom-free periods resemble miniature *petit mal* waves.

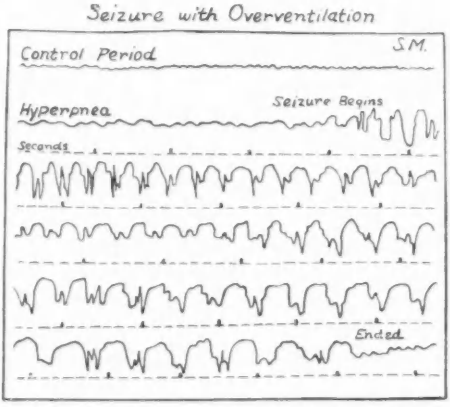


FIG. 3.—Electro-encephalogram of patient S.M. before and during hyperpnœa, and the resulting *petit mal* seizure. The upper tracing is during a conscious period. The remaining tracings are a continuous record. In the record labelled "hyperpnœa" (after the patient had been performing voluntary over-ventilation for about two minutes) the action potentials are large, slow and irregular. The seizure begins at the end of this line and continues for twenty seconds. The patient, of course, stopped over-ventilation with the onset of the seizure.

ments of the face are synchronous with the large waves. But similar movements made voluntarily by the patient when conscious are not attended by changes in the waves.

The final proof that we were dealing with brain activity was obtained by placing the needle electrode directly into brain substance. Simultaneous tracings taken from the motor area of the brain and from the scalp exhibit differences in the shape of the waves, but a momentary lapse of consciousness, when it occurs, is unmistakable in both tracings.

We have records of spontaneous *petit mal* from thirty-two patients. These records are alike in the large slow waves which replace the ten a second rhythm, but the details of the waves are individual for each patient. The waves during a portion of a *petit mal* are shown for five of the patients in the right hand panel of fig. 2. A complete *petit mal* (induced, but of the same form as this patient's spontaneous seizure) appears in fig. 3.

Of great interest is the appearance in the records of these patients (at times when they are free of any objective or subjective evidence of seizure) of small alterations in potential which are indistinguishable from the onset of that patient's seizure (fig. 2). Non-epileptic patients, when awake, never show these disturbances. We regard them as larval or subthreshold seizures. Electro-encephalograms may possibly provide a means of detecting the epileptic state of an individual, even in the absence of seizures.

We now turn to the question of the effect of changes in the physiology of the body on the electrical activity of the brain with respect to seizures. In both normal and epileptic persons the induction of alkalosis by hyperpnœa, of anoxæmia by breathing of nitrogen, or of cerebral anæmia by induced syncope, causes the action potentials of the brain to become slower and larger. When an attack is induced in an epileptic patient by one of these methods, these large waves merge into the waves of the induced seizure. The waves of the induced and of the spontaneous attack are identical. The seizure waves are clearly distinguishable by their regularity and their individual form, and especially by the sharp spike of negative potential. Fig. 3 demonstrates the alteration of electrical activity associated with a short period of hyperpnœa which was followed by seizure, and fig. 4 shows the alteration during unconsciousness from syncope together with the waves of the *petit mal* seizure which was thereby induced.

The fundamental clinical feature of an epileptic seizure is the impairment of consciousness. The states which we have been considering, acute alkalosis, anoxæmia and anæmia, also involve disturbances of consciousness. Also, in sleep, both normal and narcoleptic, and even in mental inattention, electrical potentials become larger and slower. Clinically,

all these are states which favour the occurrence of seizures. In the electro-encephalogram, it looks as though the type of electrical activity which accompanies these states integrates with and discharges the patient's neurological seizure mechanism.

What is the meaning, in terms of cerebral activity, of these large slow waves? One possible view is this. In normal activity, there are many clusters of neuronal cells discharging, not in unison, but in harmony. The usual rhythm of 10 to 20 discharges a second is a mosaic of the activity of many centres. In a *petit mal*, many waves become one. The large waves represent not a suppression or an augmentation, but rather a synchronization of various discharging cell

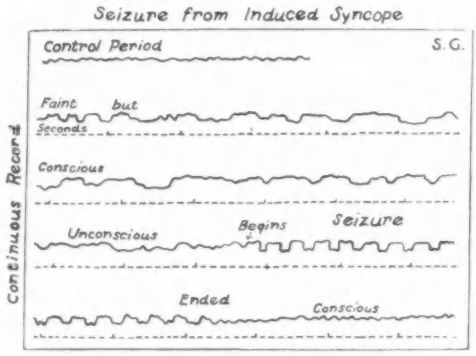


FIG. 4.—Electro-encephalogram of patient S. G., before and during syncope and the *petit mal* seizure. He was given four grains of sodium nitrite by mouth and after fifteen minutes was stood upright. The last four tracings are a continuous record. During the first tracing he was pale and faint but conscious. Within several seconds after losing consciousness, a *petit mal* attack, recognized by twitching movements of the eyebrows, began and lasted five seconds. As soon as he was unconscious, he was placed in a horizontal position and with the cessation of the seizure was again conscious.

clusters. There is integration of activity as regards timing, but disintegration as regards the delicate and complicated interplay of various discharging nuclei. The harmony of the symphony orchestra has become a single note. The representative constitutional government has become a totalitarian state.

What is the origin of this sudden synchronization in which the individuality of discharging nuclei is lost? It cannot be primarily any organic disease of the brain because structural defects are constant, whereas seizures are periodic. There must rather be transient alterations either in the pathways taken by nerve impulses, or in the electrical activity of certain clusters of cells. There is growing evidence of an

essentially neural mechanism capable of producing unconsciousness and muscle spasm without the intervention of physiological changes which involve the whole brain. I am thinking especially of cases of reflex epilepsy, of unconsciousness from an irritable carotid sinus, without circulatory changes, and of experimental evidence provided by F. A. and E. L. Gibbs [9], that certain areas of the brain have a very low threshold for convulsions electrically induced. We hope further study will disclose the point of origin and the pathway of spread of the electrical potentials associated with seizures. In conclusion, our hope of learning the pathogenesis of epilepsy, so far as it concerns physiology and so far as it has therapeutic approach, rests on finding the physico-chemical process involved in the electrical activity of the neurone. We can hardly expect to arrive at the solution of this problem, which is so closely linked in epilepsy with the mysterious problem of heredity. Yet we have our rewards. "To journey hopefully," said Stevenson, "is a better thing than to arrive." We therefore travel with hope on this long and winding road, the end of which is the end of epilepsy.

REFERENCES.

[1] Gibbs, F. A., Lennox, W. G., and Gibbs, E. L. "Cerebral Blood Flow Preceding and Accompanying Epileptic Seizures in Man," *Arch. Neurol. and Psychiat.*, 1934, **32**, 257.

[2] Lennox, W. G., and Gibbs, E. L. "The Oxygen Saturation of the Arterial Blood in Epilepsy," *Ibid.* (In press.)

[3] *Idem.* "The Blood Draining the Brain and the Limbs of Epileptics with Reference to its Oxygen Saturation," *Ibid.* (In press).

[4] Lennox, W. G. "The Effect on Epileptic Seizures of Varying the Composition of the Respired Air," *Journ. Clin. Investigation*, 1928, **6**, 23.

[5] Lennox, W. G., and Cobb, S. "Epilepsy from the Standpoint of Physiology and Treatment," Baltimore, 1928.

[6] Lennox, W. G., and Behnke, A. R., Jr. "The Effect of Increased Oxygen Pressure on the Seizures of Epilepsy," *Arch., Neurol. and Psychiat.* (In press.)

[7] Lennox, W. G. "The Multiple Causes of Seizures in the Individual Epileptic Patient," *New England Journ. Med.*, 1933, **209**, 386.

[8] Gibbs, F. A., Davis, H., and Lennox, W. G. "The Electro-Encephalogram in Epilepsy and in Conditions of Impaired Consciousness," *Arch. Neurol. and Psychiat.*, 1935, **34**, 1133.

[9] Gibbs, F. A., and Gibbs, E. L. "The Convulsive Threshold of Various Parts of the Cat's Brain," *Arch. Neurol. and Psychiat.*, 1935, **35**, 109.

THE ANATOMICAL LOCALIZATION OF THE HYPOTHALAMIC CENTRE FOR THE REGULATION OF TEMPERATURE.[1]

BY C. H. FRAZIER, BERNARD J. ALPERS AND F. H. LEWY (PHILADELPHIA).

Introduction.

It has been abundantly shown that the hypothalamus is important for the normal regulation of body temperature. The evidence for this has been reviewed so frequently in recent years that it hardly bears repetition (Bazett, Alpers, Erb [1]). While Isenschmid and Krehl [2] and Isenschmid and Schnitzler [3] indicated that it was necessary to maintain intact the hypothalamus in order to maintain normal body temperature, they failed to specify definitely the exact region of the hypothalamus necessary for this control. Furthermore, as will be seen subsequently, the area which they indicate differs with our findings. Some attempt was made to locate more specifically the temperature regulating area in the hypothalamus by Bazett, Alpers and Erb, who found in cats that the area in the walls and floor of the third ventricle was most essential for this function. This was carried still further by the studies of Alpers [4], who studied two cases of tumour in the pituitary area in which death was accompanied by severe hyperthermia and loss of temperature control. In these cases it was found that the lesions were in the floor of the third ventricle, more particularly in the substantia grisea. The more lateral and dorsal portions of the hypothalamus were intact.

On the basis of these observations, further experimental studies were undertaken in cats in order to determine whether lesions placed in the substantia grisea in the floor of the third ventricle would produce loss of temperature control. It is these experiments which we now record.

Technique.

Cats were used exclusively. They were anæsthetized with sodium amytal injected into the abdominal cavity. The cat was then fitted into

[1] From the Laboratories of Neurosurgery and Surgical Research in the University of Pennsylvania. Read before the Second International Neurological Congress, London, August 29 to September 3, 1935. This research was aided by a grant from the Rockefeller Foundation.

a Horsley-Clarke frame and measurements made for destruction of the substantia grisea of the third ventricle. Under aseptic precautions two trephine holes were made in the skull, and through these an electrode was introduced and minute lesions made bilaterally in the floor of the third ventricle. The spherical model of the Horsley-Clarke machine was used. This permitted an approach to the desired part from all angles. The animals were then placed in a specially prepared room with constant temperature and humidity. Temperature readings were made daily. The response of the cats to elevation and depression of temperature was studied. The former was observed by placing some of the animals in an autoclave for five to ten minutes and studying their temperature and the respiratory responses. The latter was studied by exposing the animal to a temperature of 2-6° C., observing the temperature, shivering, and vasomotor responses. The autoclave experiment was abandoned in our later animals, and the response to elevation of temperature studied by raising the temperature of the control room. In all instances the animals were sacrificed by chloroform anæsthesia and the brains removed without delay. Serial section studies were made of the brain-stem, alternate sections being stained with hæmatoxylin-eosin and Weil's myelin sheath stain.

Experimental Results.

Thirty cats were operated on. In only a small number of these were the lesions placed exactly in the desired situation. In most of the animals the lesion was either too far lateral in the hypothalamus or it

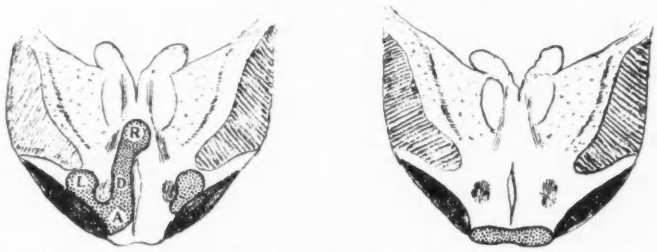


Fig. 1.—On the left diagram the dotted areas show the regions which can be destroyed without loss of temperature control. On the right the dotted area, occupying the main position of the N. anterior hypothalami, is indispensable for normal regulation of temperature.

was unilateral. In those instances in which the lesions were properly placed, the loss of temperature regulation was complete. Cat 13/10 affords an excellent example of this. In this animal the lesions were

placed in the floor of the third ventricle. This animal had total loss of temperature control: it was completely thermolabile. At room temperature its rectal temperature was 24° C. (Table I). In a warm room with a temperature of 32° C. its temperature rose to 38° C., and fell to 34° C. after twenty minutes exposure in a cold room at 2·5° C. The temperature continued to fall in the cold room, so that after five hours it was 15° C. There was no hyperpnœa, no true panting and no evidence whatever of shivering. Vasomotor responses in the foot-pads were totally lacking. Necropsy revealed bilateral lesions in the floor of the third ventricle. These proved on serial section of the hypothalamus to involve the substantia grisea of the third ventricle. The other hypothalamic nuclei, the N. paraventricularis, the N. supraopticus, the N. lateralis hypothalami, and the N. mammillaris were all intact. There were discrete lesions only in the substantia grisea.

TABLE I.

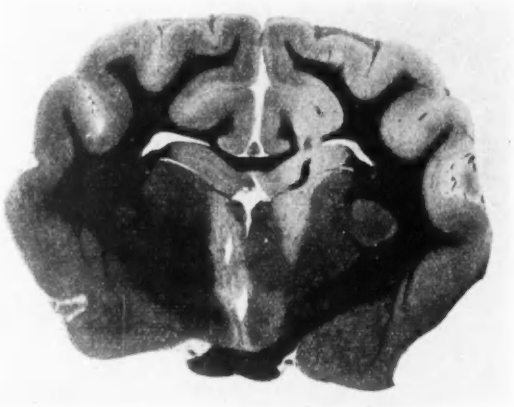
Post-operative day	Environmental temp.	Cat temp.	Pulse	Resp.	Remarks
1	27° C.	24° C.	Irregular	6	Stuporous.
2	32° C.	38° C.	140	21	Cat active. Bites and scratches. No hyperpnœa.
	2·5° C.	36° C. (after 12 min.)	124	19	
		34·5° C. (after 20 min.)	92	18	No shivering response.
	Room temp.	38·5° C.			
4	2° C.	30° C. (after 2 hrs.)	96	30	
		15° C. (after 6½ hours)	Not perceptible	Not perceptible	No shivering response.

Responses of cat 13/10 to heat and cold. There is complete thermolability with no hyperpnœic or shivering response.

Cat 13/10 represents a typical example of complete temperature loss, and is characteristic of animals in which the temperature-regulating area has been effectively destroyed. In this animal serial section studies of the hypothalamic area revealed a complete destruction of the N. hypothalamicus anterior (Rioch) or the substantia grisea which lies in the floor of the third ventricle. The destroyed area extended from the anterior part of the optic chiasm to the infundibular region.

In animals in which the lesion was not placed so as to cause a complete loss of temperature control, there were manifestations of partial loss. Cat 10 was a case in point. This animal survived five days after operation. It had a markedly subnormal temperature for twenty-four hours after operation. There was a moderate thermolability which was

seen more definitely in a hot than in a cold environment. In the hot-moist control room the temperature and respiration rose definitely. It dropped moderately in the cold room. There was never a complete



A

B

FIG. 2.—Cat 13/10 showing bilateral lesions in the hypothalamus with involvement of the substantia grisea. There was complete temperature loss in this animal.

loss of control because both hyperpnœic and shivering responses could be elicited at some times, but not at others. There was, therefore, in this cat a disturbance in heat control on both the heat-loss and heat-

producing sides, but only of a relative nature. In contrast to Cat 13 10, the necropsy in Cat 10 revealed a unilateral lesion in the anterior part of the hypothalamus destroying the median portion of the thalamus, the N. reuniens and the N. anterior hypothalamici. The lesion extended laterally in its lower portions and did not involve the grey matter in the

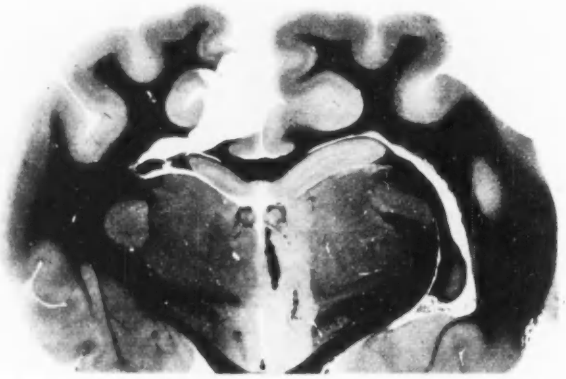


FIG. 3.—The unilateral lesion of the hypothalamus (Cat 10) with only minor disturbances in temperature control.

floor of the third ventricle. This is an instance, therefore, of a minor disturbance in temperature produced by a unilateral lesion which involved the lateral portions of the hypothalamus, and spared in part the vital area which is important for temperature control, the substantia grisea.

TABLE II.

Post-operative day	Environmental temp.	Cat temp.	Pulse	Resp.	Remarks
1	25·0° C.	25·5° C.	88	12	
	5° C.	25·5° C. (after 6 min.)		16	Definite shivering after 6 minutes.
		25·5° C. (after 12 min.)			
		26·0° C. (after 15 min.)	84	20	
2	28° C. (moist room)	40·2° C.	200	100	No hyperpnœa or polypnœa.
	27° C. (dry room)	39·5° C.			
	6° C.	38° C.	168	66	No shivering responses.
4	30° C.	40·5° C.	168	64	
	5° C.	38° C.	160	60	

Temperature responses in a cat (Cat 10) in which there was a unilateral lesion destroying only part of the substantia grisea and extending laterally into the hypothalamus.

That there may be relative hypothermia with disturbance of shivering and panting responses in unilateral laterally-placed lesions is

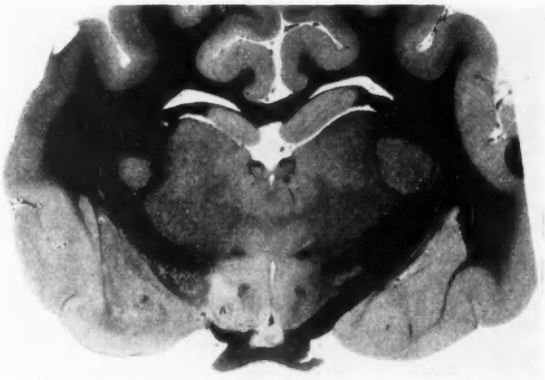


FIG. 4.—Involvement of the nucleus lateralis with only minor disturbances in temperature control.

illustrated by Cat 87, in which the lesion was in the lateral portion of the hypothalamus, not far from the vital area. This animal showed some tendency to hypothermia, with no shivering or panting responses.

TABLE III.

Post-operative day	Environmental temp.	Cat. temp.	Pulse	Resp.	Remarks
1	Room temp.	41° C.	200	40	
2	" "	34½° C.	142	24	
	5° C.	34° C.		28	No shivering.
	80° C.	32·5° C.		28	No panting.
		36° C. (after 6 min.)	156	32	No vasometer response.
4	28·5° C.	35° C.	144	24	
	5·5° C.	36° C.	180	24	No shivering.
	80° C.	35·5° C.	188	24	No panting.

A unilateral lesion (Cat 87) involving the N. hypothalamicus lateralis, with persistent hypothermia and no shivering or panting. Disturbance of temperature regulation was only relative and not complete.

Necropsy revealed a large area of necrosis involving the N. hypothalamicus lateralis (Rioch) or what corresponds in man to the N. tubero-mammilaris. The mesial portion of the hypothalamus was not affected.

It is possible, however, that the disturbance of temperature regulation recorded in Cat 87 may have been transitory, as it lived only four

days. Another animal (Cat 84) which had bilateral lesions in the N. hypothalamicus lateralis lived for nine days and revealed very little disturbance in temperature regulation. In any event, one thing seems certain from these experiments, and that is the fact that the lateral portion of the hypothalamic area is not essential for temperature regulation.

TABLE IV.

Post-operative day	Environmental temp.	Cat temp.	Pulse	Resp.	Remarks
1		39·5° C.		36	
3		38·5° C.	96	28	
	+6° C.	37° C.		24	Shivering.
	+80° C.	41° C.			Marked panting.
9		38·5° C.		28	
	5° C.	38° C.		28	Marked shivering.

A cat (Cat 84) with bilateral lesions in the lateral parts of the hypothalamus, with transitory temperature disturbances of a minor degree, which later became adjusted.

COMMENT.

Our experiments demonstrate clearly that the vital area in the hypothalamus for the regulation of temperature in cats is the N. hypothalamicus anterior, which corresponds in man to the substantia grisea in the floor of the third ventricle. Bilaterally placed lesions which destroy this tissue produce severe sustained hypothermia with a loss of function of both the heat-loss and heat-maintenance mechanisms. In no instance were we able to produce hyperthermia by lesions placed in the hypothalamus. Unilateral lesions placed in the vital area are followed by severe transitory disturbance in temperature control, but the results are not permanent.

For the complete loss of temperature control it is necessary to have bilateral destruction of the area concerned: the N. hypothalamicus anterior in cats, and the substantia grisea in man.

Laterally placed lesions in the hypothalamus, even if bilateral, are followed by only a transitory loss of temperature control, which in one of our animals was completely restored by the ninth day after operation.

Attention has been called in previous publications (Bazett, Alpers and Erb; Alpers) to the importance of the mesially located tissue in the floor of the third ventricle. While Isenschmid and Krehl indicated in general the importance of this area, their researches did not disclose the exact region necessary for temperature control in the hypothalamus. They asserted that in the rabbit the most important area is the tuber cinereum, stating also that the region close to the third ventricle is of no greater importance for the regulation of temperature than those more

distant. Our findings are in disagreement with this. There appears to be no question that the mesial portions of the hypothalamus in the floor of the third ventrical are most vital for temperature control. The lateral portions are not in themselves essential.

Conclusions.

(1) Mesially placed bilateral lesions in the floor of the third ventricle by means of the Horsley-Clarke apparatus produce complete loss of temperature control.

(2) Laterally placed lesions, whether bilateral or unilateral, cause only transitory and fleeting disturbances of temperature regulation.

(3) The vital area for temperature regulation in the hypothalamus is in the floor of the third ventricle, corresponding to the N. hypothalamicus anterior in cats and the substantia grisea in man.

BIBLIOGRAPHY.

[1] Bazett, H. C., Alpers, B. J., and Erb, W. H. "Hypothalamus and Temperature Control," *Arch. Neur. and Psych.*, 1933, **30**, 728.

[2] Isenschmid, V. R. and Krehl, L. "Über den Einfluss der Gehirns auf die Wärmeregulation," *Arch. f. Exper. Path. u. Pharmacol.*, 1912, **70**, 109.

[3] Isenschmid, V. R., and Schnitzler, W. "Beitrag zur Lokalisation der Wärmeregulation vorstehenden Zentralapparates in Zwischenhirn," *Ibid*, 1914, **76**, 202.

[4] Alpers, Bernard J. "Hyperthermia due to Lesions in the Hypothalamus," to be published in *Arch. Neur. and Psych.* Read at American Neurological Assoc., Montreal, May, 1935.

Notices of Recent Publications.

Handbuch der Neurologie. Herausgegeben von O. Bumke und O. Foerster. Berlin: Springer, 1936.

Five more volumes of this system have appeared. They are so comprehensive that in a review it is possible to indicate only their contents.

Band XVII: *Erkrankungen des Rückenmarks und Gehirns.* S. 575, mit 24 Abbildungen. Price RM. 93.

This volume opens with a long article in English by Kinnier Wilson on "The Epilepsies," in which convulsions are treated as merely symptoms of morbid states whether we can identify these or not. The subject is presented with the clarity and completeness which would be expected of the author. In his chapter on narcolepsy Wilder discusses this interesting subject very fully from the clinical as well as the physiological point of view. Under the title spasmophilia Husler deals with tetany and with other less-defined forms of spasm and convulsions. The clinical features of migraine, their pathogenesis, and their treatment are admirably dealt with by H. Richter of Budapest. He favours the view that the attacks result from angiospastic crises, possibly due to various factors, of the cerebral vessels of the vertebral system. The chapter on the vasomotor and trophic affections, including Raynaud's disease, erythromelalgia, acrocyanoses, acroparæsthesiæ, scleroderma and allied conditions, was originally written by Cassirer but has been revised by R. Hirschfeld. Each of these subjects is excellently presented and the latest investigations on them are incorporated.

Braun analyses and describes some of the commoner psychoneurotic disorders under the heading "Die neurasthenische Reaktion," allotting due importance to both their mental and physical aspects. In the last chapter Jahrreiss of Cologne deals with the so-called organic neuroses, which he defines as the "psychogenesis of bodily disturbances." He discusses in the first place the disorders of the vegetative system which are attributable to mental factors, and finally the occupational neuroses and stammering.

XII u. XIII Bänder: *Infektionen und Intoxikationen.* Bd. XII. S. 776, mit 133 Abbildungen. Price 132 RM; Bd. XIII. S. 1116, mit 212 Abbildungen. Price RM. 192.

These two volumes deal very comprehensively with nervous diseases of infective and toxic origin. The greater part of the first is devoted to syphilitic disorders. Sarbó contributes an excellent article on meningo-vascular affections in acquired and congenital syphilis, but he has devoted so much space to their

pathology and to the citation of authorities that the definition of clinical types has suffered. Richter writes on the pathology of tabes dorsalis, maintaining still that the essential cause is development of granulation tissue in the subarachnoid space around the dorsal roots, but he gives adequate attention to other views. Mann deals with the clinical aspects of tabes and its treatment, and Jahnel with general paralysis and trypanosomiasis. Sittig describes in great detail the tubercular diseases of the nervous system, including, in addition to generalized meningitis, circumscribed tubercular meningitis, pachymeningitis tuberculosa, and serous meningitis associated with tuberculosis. Kroll, of Moscow, writes on leprosy and on the nervous complications of typhus fever, and Gamper on chorea. The volume opens with a short chapter on the nervous complications of the exanthemata and of other infectious illnesses.

The first half of Volume XIII is devoted to diseases due to filtrable viruses in which myelitis and disseminated sclerosis are included. Wohlwill deals with herpes zoster, Kroll with rabies, and Pette with the symptoms and anatomical changes in poliomyelitis and postvaccinal encephalitis. The latter section contains a valuable discussion to the nature of acute disseminated encephalomyelitis. Stern, a recognized authority on the subject, writes on epidemic encephalitis, including the allied diseases which have occurred in Japan, Australia, and elsewhere. Köryey discusses myelitis, excluding that due to syphilitic and other recognized pathological agents; consequently, he concentrates mainly on the acute disseminated type. Marburg deals in a masterly manner with the clinical and pathological features of disseminated sclerosis, which he regards as an infectious disease due probably to a virus. The second part of this volume consists mainly of exhaustive articles by Bumke and Krapf on the action of exogenous poisons on the nervous system, and by Bumke and Kant on acute intoxications and drug addictions. Other chapters deal with nervous affections due to metabolic disturbances, diseases of the blood and nutritional disorders; they include a concise but adequate article by Bremer on subacute combined degeneration of the cord, or, as he calls it, funicular myelitis.

Band IX: *Muskeln und Periphere Nerven.* 1935. S. 259, mit 57 Abbildungen. Price RM. 45.

This volume opens with a short but useful chapter on myalgia and myositis by Moser. Wexberg writes on the symptoms and pathology of traumatic lesions of the peripheral nerves and plexuses and on the principles of their treatment, and in a later chapter on neuritis and polyneuritis; in the latter section he includes facial palsy, sciatica, and special affections of other peripheral nerves. The chapter on the neuralgias, also written by Wexberg, is concise but comprehensive; treatment is excellently described. The histology of neuritis is dealt with by Villaverde of Madrid, and tumours of the peripheral nerves by Gagel; both these sections are well illustrated and incorporate the latest views on the pathology of the somatic and sympathic systems.

Band VIII: *Allgemeine Therapie.* S. 749, mit 182 Abbildungen, Price RM. 126.

This volume opens with a concise but valuable chapter by Fröhlich on the pharmacology of drugs which influence the nervous system. In the next Wagner-Jauregg writes on treatment of general paralysis and disseminated sclerosis by induced fever. Lehmann deals exhaustively with the surgical treatment of injuries and diseases of the central and peripheral nervous systems, including the sympathetic, and Hohmann with the orthopædic treatment of palsies. Foerster devotes 100 pages to "Uebungstherapie," that is, the correction or compensation of various motor disturbances by exercise and re-education; he analyses the factors on which success depends and describes fully the methods applicable to different conditions. It is an extremely valuable and unique presentation of the subject. Mann deals at considerable length with electrotherapy, Marburg and Sgalitzer with radiotherapy, Strasser and Wexberg with the influence of baths and climate, and Reinhold with psychotherapy.

All the sections of this important volume, which can be strongly recommended to all neurologists, attain a high standard.

On the Peroneal Type of Progressive Muscular Atrophy. By JULIA BELL. The Treasury of Human Inheritance, Cambridge University Press, 1935. Vol. IV., "Nervous Diseases and Muscular Dystrophies," Part II. Pp. 70, with plates and pedigrees. Price 12s. 6d.

This study contains an account on the usual lines of the clinical course and features of peroneal muscular atrophy. The author notes that the paresis and limitation of movements are in proportion to the muscular wasting, but most observers would maintain that a characteristic of this disease is the mobility which sufferers from it retain for years after profound muscular atrophy below the knees has been present, and much deformity of the feet has developed.

There is a list of other abnormal physical signs in the nervous and other systems that may be found in cases of peroneal muscular atrophy, but no information is given to show whether or not these are simply coincidental phenomena, and no conclusions can be drawn from their presence.

Peroneal atrophy may, it appears, exhibit every type of inheritance, and the author classifies her pedigrees under three headings: Group A, representing sex-linked inheritance, Group B, in which both parents are normal, and Group C, of dominant inheritance in which one or other parent has been affected and the sufferers themselves—whether male or female—are liable to have affected offspring. The large majority of cases of peroneal atrophy fall into Group C.

The study is very diffusely written and expensively produced, and its high cost will seriously limit its circulation amongst those from whom its readers

might expect to be drawn. The investigations of which the present study is one, are of great interest to neurologists, and their publication in a more succinct and less expensive form would be widely welcomed.

Études Neurologiques. Par G. GUILLAIN. 6 ième série. Paris: Masson et Cie. 1935. Pp. 430. Price 80 francs.

Those who have enjoyed the previous volumes of this series, with their clinico-anatomical approach to the problems of neurology, will welcome this addition thereto. It covers a wide range of nervous diseases, and includes a long chapter on intracranial tumour as well as shorter studies of cerebral, spinal, peripheral nerve and muscular diseases.

Perhaps the most interesting chapter deals with occupational paralyses of the external popliteal division of the sciatic, and illustrates the anatomical relationships in the region of the knee which is responsible for the paralysis.

The Image and Appearance of the Human Body, By P. SCHILDER, Psyche Monograph No. 4. London: Kegan Paul. 1935. Pp. 353. Price 10s. 6d.

Dr. Schilder's ability in fusing theories and observations here results in a fluent and coherent account of the part the body-schema can be conceived to play in a physiological psychology. Head and Freud are the two chief sources of his theory, though Goldstein, Köhler and many others have also been laid under contribution. It is not the views he presents, but the boldness and dexterity with which the author moulds them together that gives the work its original and interesting flavour.

Psycho-analytic interpretations of human conduct and thought are so essential to his thesis that the non-Freudian reader will find the book a stimulating essay rather than a report of an empirical investigation, which it is intended to be.

Chagrins d'amour et psychoses. Par CONSTANCE PASCAL. Paris: G. Doin. 1935. Pp. 168. Price 16 francs.

The authoress here carries her previous work on emotional shocks into one of the most difficult fields that could well be found. Like every psychiatrist she is familiar with some of the effects of unhappiness in love, but to add to what has already been said on the topic is beyond her powers.

The style of her readable book is less sober than is usual in psychiatry; along with descriptive sections on morbid syndromes and case histories there is critical and largely adverse examination of current psychological theories.

Objective and Experimental Psychiatry. By D. E. CAMERON. New York: Macmillan. 1935. Pp. 271. Price 12s. 6d.

This compilation arose out of the author's distrust of purely descriptive and intuitive concepts of human behaviour. His chapters are brief reviews of some of the American and English publications on disconnected psychiatric topics which have been dealt with experimentally or statistically; methods and findings are discussed. The book lacks the essential qualities of scope and judgment. Investigations published in other languages than English are barely mentioned, discredited work is occasionally reported without the necessary indication of its shortcomings, and in several fields the author shows an unfamiliarity that leads him to omit important studies. In spite of the laudable purpose and outlook set forth in the beginning of the book, it would have been better if less ambitious and more selective.

Zur Genealogie psychopathischer Schwindler und Lügner. VON W. VON BAEYER. Leipzig: Thième. 1935. Pp. 234. Price M. 16.

This study is concerned with the families of sixty-seven psychopaths who had been admitted to the psychiatric clinics of Heidelberg and Munich because of a characteristic tendency to cheat and lie. The incidence of mental disorder of every sort, epilepsy, defect, drunkenness and criminality among their brothers and sisters, parents and cousins is reported in a series of tables and a lengthy text occupying half the monograph. The other half is devoted to detailed case reports of some of the patients, and sketches of their relatives' lives. The author had to cope with great difficulties both in the collection of the material and in its evaluation. He concludes that the patients, although divisible into two main groups, all show the hysterical type of character. He describes them further as "loose" (ungebunden) and inclines to the view that what is inherited in them is a predisposition to this "looseness" in the structure of character: the evidence for this is stated at length.

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EDITOR.